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THE ESTIMATION OF DRY SKELETAL WEIGHT BY PHOTOMETRY OF ROENTGENOGRAMS

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THE measurement of body composition in living man has improved considerably in the last few years. Perhaps the most important new measurement is the estimation of body fat by x-ray and specific gravity techniques. These methods permit one to quantify the fat and the fat free portion of the body. The use of biochemical techniques has increased our knowledge of body composition by providing measurements such as total body water, extracellular fluid and plasma volume. One of the major obstacles in our present estimate of body composition is a quantification of skeletal weight. While biochemical methods are available to determine whether one's bone mineral content is increasing or decreasing, no accurate method exists for providing an estimate of the total amount of bone present in the human body. In addition, bone mineral changes cannot, at present, be judged relative to the amount of bone present at the beginning of a balance study.

An anatomical approach has been utilized to estimate the skeletal weight by Merz *et al.* ('56) who have shown that there is a relationship between the weight of the dry, fat free skeleton and stature, femur length, area of the shaft and area of the compact bone in the femur

midshaft. However, the use of all these independent variables provides a prediction equation which has a standard error almost equal to the standard deviation of skeletal weight. This permits the prediction of only three effective categories of skeletal weight: light, average and heavy. An analysis of the independent variables mentioned above indicated that the most significant one was the area of compact bone in the midshaft of the femur. This is to be expected since Trotter ('54) has shown that of all the single bones in the skeleton, the femur is the best correlated to total skeletal weight. Presumably the area of compact bone in the midshaft has a reasonably high relationship to total femur weight.

Investigations by McFarland ('54) with the bone density computer at Pennsylvania State University had indicated that the apparatus might give accurate measurements of the amount of mineral present in a bone section which had been x-rayed in the proper manner with a special aluminum alloy wedge. This suggested to the present investigators that a more accurate prediction of skeletal weight could be derived using this technique. The present paper reports the progress to date in developing a method for predicting the dry skeletal weight of a man from x-rays of his upper arm and thigh.

The equipment and its operation

The bone density computer consists of a tracing microdensitometer, an integrating device, mass counters, and a data recording device. To determine the density of a bone, a roentgenogram of the bone and calibration wedge is placed in the film holder. The images of the bone and wedge are traced along a predetermined straight line called a trace path: the wedge along a line parallel to its length and the bone along any desired line. The light passing through the wedge during the tracing process strikes a photomultiplier tube, light energy is thereby translated into an electrical signal. The signal is a monotonically increasing function of the wedge slope which is constant. This signal, at any instant, represents the total mass of the minute portion of wedge which the light beam traverses at that instant. By the use of an electromechanical integrating device, these signals are summed and presented in the form of a number which is a function of the total amount of wedge traced.

Inasmuch as the physical properties (density, composition, dimension) of the wedge are known, the number which represents the total mass count of wedge traced is directly related to a known quantity of aluminum alloy.

The most critical function of the integrating device is the adaptation of the densitometer: 1.) to variation in roentgenographic technique (exposing and processing film) and 2.) to the non-linear response of x-ray film to changes in x-ray intensity. This adaptation is effected by assigning an increasing step-series of specific number values to increasing film densities. This procedure determines that, when the bone is being traced, a given film density will be interpreted as a certain mass of aluminum alloy. Finally, a total mass count is obtained from the bone trace by a summing process in terms of a total mass of aluminum alloy. This mass count may be interpreted as a bone mass, since both bone and wedge can be described in terms of atomic content and x-ray mass absorption coefficients. The tracings of a femur and humerus cross section are illustrated in figure 1.

To convert these readings to bone density, an estimate of the volume of the cross section traced must be made and the mass divided by the volume. For the purposes of this study, the mass was the most useful measurement. Therefore, only mass readings are reported and are designated as mass coefficients. A more detailed description of the concepts and construction of this machine are given by Brown and Birtley ('51).

Determination of the number of trace paths required to predict accurately the weight of a whole bone

Work with rat femurs indicated that when a section of bone is traced, the weight and mineral content of that section can be predicted with great accuracy (the r values were .98 or better) (Schraer and Schraer, '56). However, tracing all the possible one-millimeter wide paths on a bone such as the human femur would require many days of work. Therefore, it was desirable to determine the optimum number of paths, *i.e.*, the minimum number which will still give satisfactory correlation to dry bone weight. Eleven human femurs taken from an anatomical collection were dried to a constant weight at a temperature of 70° C. They were then weighed and x-rayed with the wedge at 55 KVP, 60 milliampere-seconds and a 40 inch focal film distance. No-screen film and cardboard holders were used. Beginning .5 cm from the distal end of the bone, a total of 21 trace paths were made between the distal end and the midshaft. After these trace paths were evaluated twice, the 42 mass coefficients for each femur were averaged and correlated to the total femur weight. Four paths were then selected from the 21 and correlated to the weight, and, in addition, the midshaft tracing alone was correlated

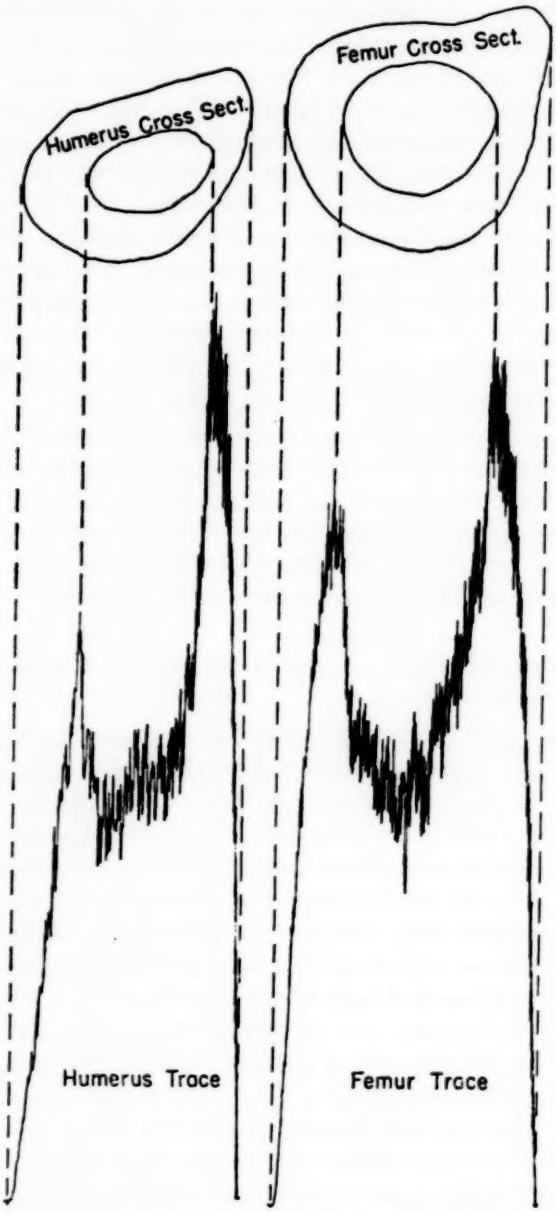

FIG. 1. DENSITOMETRIC TRACES OF A HUMERUS AND FEMUR THROUGH THE MIDSHAFT: SCALE OF FEMUR AND HUMERUS DIFFERENTIALLY EXPANDED FOR ILLUSTRATIVE PURPOSES. IN PRACTICE EACH TRACE IS RELATED TO THE WEDGE TRACE TAKEN FROM EACH FILM.

to weight. The relationship of the x-ray mass coefficients to the femur weight are shown graphically in figure 2. When twenty-one trace paths and four trace paths were used, the correlation coefficient (r) was .98 in both cases. This value was lowered to .94 when one trace path was used. Four trace paths on the distal half of the femur appear to be the maximum required for an accurate estimate of its weight. However, each trace on a femur requires about 15 minutes of machine time. Thus,

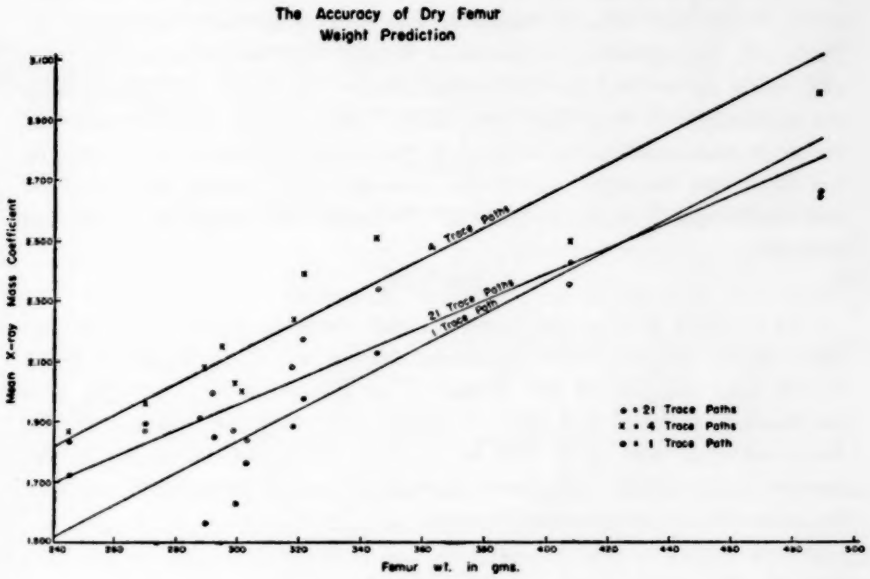
The Accuracy of Dry Femur Weight Prediction
Mean X-ray Mass Coefficient
Femur wt. in gms.
4 Trace Paths
21 Trace Paths
1 Trace Path
• = 21 Trace Paths
x = 4 Trace Paths
• = 1 Trace Path

FIG. 2.

one midsection trace path appears to provide sufficient information for routine evaluations, particularly when working with a group or with between-individual variations where maximum sensitivity is not required. When more accuracy is required four trace paths should be evaluated.

The relationship of femur and humerus x-ray mass coefficients to total dry skeletal weight

SAMPLE AND METHODS

The human skeletal material used to determine the relationship of x-ray mass coefficients to total dry skeletal weight consisted of Korean War Dead and has been previously described (Baker and Newman,

'57). Along with the measurements described in the previous publication, roentgenograms of the right femur and humerus were made using the wedge. These plates were 8 by 10 Kodak no-screen film, enclosed in cardboard cassettes. The matched femur and humerus were placed with the anterior aspect facing the cassette and, after centering the x-ray tube 60 inches above the midpoint of the bones, the plates were exposed at 55 KVP for 324 milliampere-seconds. The midpoints on both bones were determined from the maximum length as measured on an osteometric board and were indicated on the x-ray plate with a lead arrow. These roentgenograms were processed through the bone density computer and, using the method previously described, a transverse tracing through the midsection of both bones was made. This process was repeated and the x-ray mass coefficients reported in this paper are the average obtained for these two tracings. After the elimination of poorly exposed films and unidentified cases, a total of 78 individuals were available for analysis.

RESULTS

An analysis of the component skeletal parts, as reported in the previous paper, indicated two significant factors which produced variation in the bone weights of the Korean War Dead material. These were the manner of burial and race. For this study only the Prisoner of War Dead material was used, and negro and white skeletal material was analyzed separately. The basic demographic and derived statistics on the material are summarized in table 1.

TABLE 1

Demographic and derived statistics on the populations

	White $N = 64$		Negro $N = 17$	
	MEAN	S. D.	MEAN	S. D.
Age (yrs/mos)	25/5	6/2	26/4	3/8
Body Weight (kgs)	70.67	12.66	65.90	6.66
Height (cms)	173.6	6.6	173.9	5.9
Dry Skeletal Weight (gms)	4258.7	615.6	4583.0	441.6
Dry Femur Weight (gms)	409.2	62.5	423.9	41.6
Dry Humerus Weight (gms)	152.4	23.8	168.1	20.2
Femur Length (cms)	47.0	2.4	48.1	2.0
Humerus Length (cms)	33.5	1.7	33.8	1.7
Femur X-ray Mass Coefficient	2.519	.320	2.462	.194
Humerus X-ray Mass Coefficient	1.435	.226	1.512	.177

The femur and humerus were chosen for roentgenographic analysis for two reasons: first, they form a large portion of total skeletal weight and were shown by Trotter to be highly correlated to total dry skeletal weight ('54); second, because of their geometry they are fairly simple sites for densitometric analysis. As shown in table 2 the simple correlations of femur and humerus weight to total dry skeletal weight were not as high as those reported by Trotter. This may be due to the difference between burial and anatomical collection material. However, if the weight of both bones is correlated to the total skeletal weight by a multiple correlation, adequate prediction equations may be derived. Consequently, if the weight of these bones is accurately predicted, a usable estimate of total dry skeletal weight may be derived.

TABLE 2

The correlation of femur and humerus weights to total dry skeletal weight

	Whites		Negroes	
	Zero order	Multiple	Zero order	Multiple
	r	R	*r*	R
Humerus Weight	.84	.93	.61	.83
Femur Weight	.89		.83	

The correlation of the x-ray mass coefficient of the individual bone to its weight was not as high as the preliminary tests on the anatomical series had suggested it would be. The femur mass to weight correlation coefficients were .81 for whites and .80 for the negroes. The humerus mass to weight correlation coefficients were .85 for whites and .74 for negroes.

In attempting to predict the total dry skeletal weight the bone lengths were also considered, as it was found by Merz *et al.* ('56) that these lengths sometimes improved prediction. Table 3 shows the simple and multiple correlation values which were obtained. The individual plots of x-ray mass coefficients in relationship to total dry skeletal weight are shown in figures 3 and 4.

In this sample the correlations indicate that the x-ray mass coefficients appear to be adequate predictors of total dry skeletal weight. The addition of femoral and humeral lengths do not substantially improve the multiple correlation coefficients for either the whites or the negroes. The lower multiple correlation coefficients found for the negroes are probably

a product of the very limited range of bone weights encountered in this small sample. However, the samples could not be combined, as the negro and white regression slopes for bone weight to skeletal weight were divergent. This may be explained by the higher skeletal weight

TABLE 3

The intercorrelations of the predictive factors and their multiple correlation to total dry skeletal weight

	HUMERUS X-RAY MASS COEFFICIENT	FEMUR LENGTH	HUMERUS LENGTH	TOTAL DRY SKELETAL WEIGHT	MULTIPLE CORRELATION TO DRY SKELETAL WEIGHT	
WHITES						
Femur X-ray Mass Coefficient	.548	.316	.330	.775	.862	.887
Humerus X-ray Mass Coefficient		.079	.043	.735		
Femur Length			.882	.362		
Humerus Length				.360		
NEGROES						
Femur X-ray Mass Coefficient	.165	.596	.105	.603	.716	.729
Humerus X-ray Mass Coefficient		—.209	—.199	.479		
Femur Length			.679	.291		
Humerus Length				.108		

of the negroes and the differing x-ray mass coefficients. The samples showed that the negroes as compared to whites had a higher mean x-ray mass coefficient for the humerus, while they had a lower mean value for the femur.

The regression equations for predicting total dry skeletal weight from various characteristics of the femur and humerus are given in table 4.

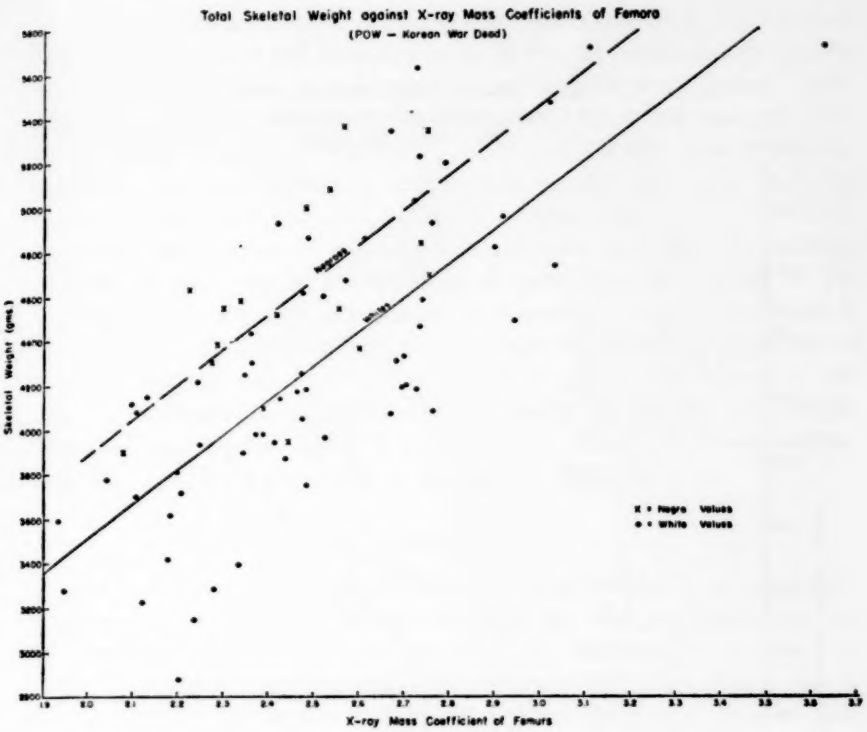
Total Skeletal Weight against X-ray Mass Coefficients of Femora
(POW — Korean War Dead)
Skeletal Weight (gms.)
X-ray Mass Coefficient of Femurs
X = Negro Values
• = White Values

FIG. 3.

TABLE 4

Regression equations for predicting total dry skeletal weights

WHITES
Total dry skeletal weight = 2106.3 humerus x-ray mass coef. + 1272.8± 401.0
Total dry skeletal weight = 1567.6 femur x-ray mass coef. + 345.7 ± 426.0
Total dry skeletal weight = 1057.6 femur x-ray mass coef. + 1267.6 humerus x-ray mass coef. — 188.2 ± 323.9
Total dry skeletal weight = 2174.9 + 871.6 femur x-ray mass coef. + 1320.8 humerus x-ray mass coef. + 1514 femur lg. + 4.937 humerus lg. ± 295.3
NEGROES
Total dry skeletal weight = 1181.2 humerus x-ray mass coef. + 2812.9 ± 378.1
Total dry skeletal weight = 1346.6 femur x-ray mass coef. + 1283.5 ± 344.0
Total dry skeletal weight = 1191.8 femur x-ray mass coef. + 947.3 humerus x-ray mass coef. + 232.7 ± 301.7
Total dry skeletal weight = — 900.9 + 1368.9 femur x-ray mass coef. + 917.9 humerus x-ray mass coef. — 2.251 femur lg. + 5.182 humerus lg. ± 302.1

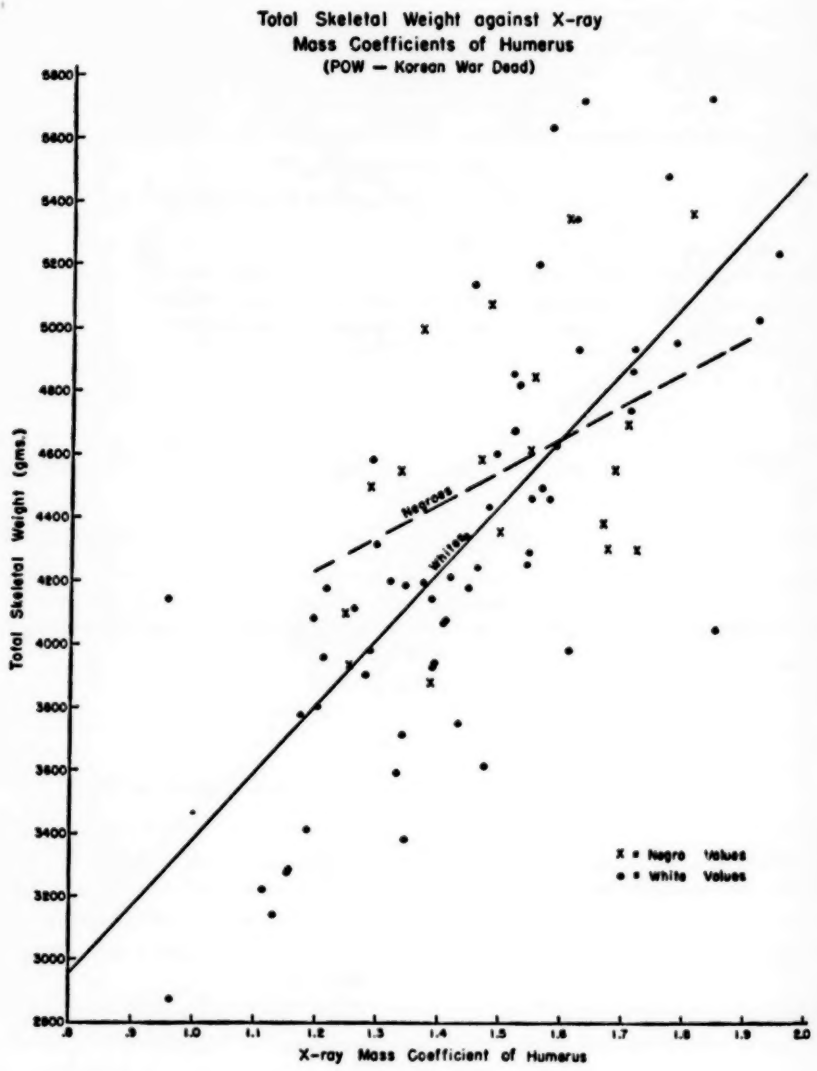
Total Skeletal Weight against X-ray
Mass Coefficients of Humerus
(POW — Korean War Dead)
Total Skeletal Weight (gms.)
X-ray Mass Coefficient of Humerus
Negroes
Whites
x = Negro Values
• = White Values

FIG. 4.

Although the correlation coefficients for the whites were much higher, it will be noted that the standard error of the predicted skeletal weight has approximately the same absolute value for both racial groups, again suggesting that the negro multiple correlation (R) values were governed by the small range of the skeletal weights. This low prediction error also hints that the regression equations for predicting Negro total dry skeletal weights are possibly as accurate as those derived for the whites. However, the number of cases used is so small that the extrapolation from this sample would be tentative, at best. For the whites, if the formulae including both x-ray mass coefficients are used, the standard error of the prediction is less than half of the standard deviation of skeletal weights. A slight improvement is gained by including the lengths. However, the improvement is small, and as the total length of these bones on the living is a difficult and inaccurate measurement, it seems better to use only the x-ray mass coefficients.

DISCUSSION

The present technique for estimating skeletal weight from roentgenograms is adequate for dry skeletal material provided the individual was between 18 and 40 years of age, and male. Furthermore, it is apparently better for whites than Negroes. Merz *et al.* ('56) have shown that it would probably not be safe to extrapolate these findings to females and, while no serious error would be encountered by extrapolating to older individuals, the equations will not apply to younger people.

In order to apply this technique to living subjects it would be necessary to correct for soft tissue encasing the bones. The bone density computing machine may be used for making a reading on the mass of the tissue surrounding the bone, and by appropriate calculations a correction could be made to the formulae as they now exist and the results applied to a direct estimate of total dry skeletal weight from roentgenograms of the living man. Two sources of error would not be corrected by this technique: first, the water content and certain organic constituents inside the living bone, which were not present in dry defatted bone, may produce an error and, second, it has been pointed out that large bones and large masses of soft tissue may produce considerable scattering error (Jackson, '51).

With the construction of a scintillation counter for the measurement of bone density (Mayer, '56), Trostle was able to make a direct measurement of the scattered radiation using various human extremity bones

with, and without, ground meat surrounding them to simulate soft tissue ('57). From these studies Trostle concluded that the scattering error in measuring x-ray mass for a human extremity is less than 10% and is probably in the range of 3 to 8%; the scattering error increases slowly as the size of the object increases, and the soft parts produce most of the scattering error.

The only direct experimental evidence is the rat work reported by Schraer and Schraer ('57), who found that the femur x-ray mass readings from x-ray plates of living rats correlated .98 to the values on plates from the excised femurs.

It thus appears that a direct comparison of x-ray plates on intact and excised human femora and humeri will be required before we can be certain of the present correction techniques. A series of plates on cadavers is now being made and, when complete, should provide us with both the exact error factor related to soft tissue and a correction for any systematic error involved in the present soft tissue correction.

Trotter and Peterson ('55) have shown that for most non-pathological individuals the ashed weight of the skeleton formed 64.8% to 66.9% of the dry skeletal weight. However, they also found one skeleton where the ashed weight was only 54% of the dry skeletal weight. If this individual did not during his lifetime have some disorder that affected his bone mineral content, we must asume that dry bone weight is not always a close predictor of bone mineral even for non-pathological individuals. Work with x-ray mass coefficients for rat femur has shown that these values reflect bone ash content as closely as dry weight (Schraer and Schraer, '56). Thus, x-ray mass coefficients for human femora and humeri may be better indicators of the total bone mineral than the predictions of dry skeletal weight indicate, but the work of Trotter and Peterson ('55) also indicate that shifts in bone mineral are more common in other bones than the femur and humerus. Therefore, it appears that direct experimental work will be required before we can determine how accurately our present techniques will predict total bone ash in the body.

The presence of any pathological condition which affects bone would probably change not only the relationship of one skeletal component to another, but also the relative mass of different parts of the same bone. Thus, the present formula would probably not be accurate for any individual with an osseous disorder. Because of these limitations, we visualize this technique to have two major applications: first, it may offer an independent measure of bone weight for correcting and im-

proving measurements of body compositions; and second, it may provide a tool for investigation of the effects of nutriture and genetics on the growth and development of the skeleton.

SUMMARY

Methods of measuring body composition have improved considerably in the past few years. However, present techniques do not give any accurate method of measuring total dry skeletal weight or total bone mineral in the living man. In the present study we have shown how a reasonably accurate estimate of total dry skeletal weight may be made from roentgenograms of the humerus and femur of adult males. The material consisted of: the dry weight and x-ray plates of 11 femora from an anatomical collection; the dry, defatted total skeletal and individual bone weights of 61 whites and 17 Negroes who died in the Korean War plus x-ray plates of their right femur and right humerus. An aluminum alloy wedge which served as a standard was exposed simultaneously with the bones. The films were evaluated in the bone density computing machine, which gives a value of the mass in terms of aluminum alloy for the section of the x-ray film studied and corrects this reading for differences in the film due to variations in exposure and development.

Experiments with the 11 femora from the anatomical collection indicated that a single trace path across the midshaft was adequate to predict total femur weight. The Korean War Dead material showed that the weights of the femora and humeri would accurately predict total skeletal weight for the whites and, with limited accuracy, for Negroes. An evaluation of the x-ray film though the midshaft of these bones yielded x-ray mass coefficients which predicted the individuals' total dry skeletal weight with a standard error equal to approximately one half of the standard deviation of dry skeletal weight. The addition of bone lengths did not significantly improve the multiple correlations. These results were obtained on skeletal material and cannot be applied to the living without further modification of the technique or the derivation of a soft parts correction. The development of this correction is in progress and, if completed successfully, the estimation of dry skeletal weight should offer a valuable adjunct to our methods of measuring normal human body composition.

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SOME MONTE CARLO METHODS APPLIED TO AN EPIDEMIC OF ACUTE RESPIRATORY DISEASE

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INTRODUCTION

FOR over half a century attempts have been made to approximate the course of epidemics by the use of mathematical models. In the pioneer work on this subject many aspects of the transmission of disease were considered and many assumptions were made about such things as the virulence of organisms, susceptibility of populations, periods of incubation, and so on. The resulting epidemic curves, usually expressed by the weekly incidence of new cases, were reproduced in a wide variety of situations. Generally speaking, this early work was deterministic in nature, ignoring variation in epidemics and being applicable primarily to large populations. Reference is made to the fine review article by Serfling ('52).

Following the preliminary attempts at mathematical model building, developments by many investigators, including Greenwood ('20, '31, '36), Feller ('39, '43) and Lundberg ('40), drew attention to the use of stochastic process theory and probabilistic models in this field. As a consequence, during the past 15 years attention has been turned with increasing frequency to the study of epidemic phenomena by probabilistic methods. A series of papers by Bartlett ('49, '53, '56), Kendall ('48, '50), Bailey ('50, '53, '55, '56) and Whittle ('52, '55) report studies which were made of several simple epidemic models. In addition to information on the course of an epidemic, results have been obtained on the total size of an epidemic, on chain-type situations, on recurrent

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epidemics, and on threshold conditions leading to major or minor epidemics. One discouraging result has been the exceedingly complicated mathematical problems which come from incorporationg necessary conditions into the models. For the past 3 or 4 years a few experimenters have attempted to avoid these complications by using random sampling or Monte Carlo techniques. Recent work by Bartlett ('57) and Kendall ('56) illustrates this.

The present paper presents a probabilistic model and its deterministic counterpart which were developed to describe the course of acute respiratory disease among recruits at a former Air Force reception center at Sampson Air Force Base. Four parameters are estimated in order to fit the model to actual data, and the model is then used to create several hundred artificial epidemics. The frequency distributions of the numbers of cases per week so obtained are compared with actual observations. While patterned after the classical models studied by Bartlett, Bailey, and Kendall, this work brings in two complications not present in early models. Partial immunity and subclinical cases are admitted as possibilties and their properties are determined by fitting the model to the observations.

Epidemic situation

During the winter of 1952-53 at Sampson Air Force Base in upper New York State observations were made of the incidence of upper respiratory disease among a large number of young men newly recruited by the Air Force. See Bernstein ('57) for further description of the base. As men entered the Air Force in the eastern part of the United States they were sent immediately to this base. Upon arrival they were organized into groups, called "flights," most of which were composed of either 60 or 72 men. For 12 weeks thereafter, they lived, ate, and worked together in these flights. There was considerable cohesiveness within these groups and the members of a flight tended to stay together On the other hand, there was a mingling of men from all over the base at theaters, games, stores, and so forth. In terms of exposure, each man was exposed to infection from infected men in his own flight as well as to an additional, fairly continuous level of infection existing within the base environment.

All flights of recruits assigned to areas G and H of Sampson Air Force Base between November 1, 1952 and March 1, 1953, and consisting of 60 men each, were chosen for study in this paper. There were 117 of

these and they were observed throughout the entire 12 weeks of training. Whenever a man was hospitalized for upper respiratory disease the diagnosis was recorded. Only those diagnoses which were labeled "acute respiratory disease" (ARD) were included in this work.

ARD was defined, Bernstein ('57), as "acute illnesses with respiratory symptoms or constitutional reactions, or both, in which there was no increase in the influenza antibodies, a negative throat culture for group A streptococci, and hospitalization for less than seven days." In recent years members of a certain family of viruses called "adenoviruses" have been established as causative agents accounting for a sizeable portion of cases of ARD, Hilleman ('54, '55) and Rowe ('53, '56). Experiments using volunteer subjects, Commission on Acute Respiratory Diseases ('47), revealed that the incubation period is about 5 to 6 days, wtih fever lasting 2 to 4 days and some symptoms persisting for two weeks. While there is evidence that infection by a specific type of this virus family results in immunity to that type, such immunity does not seem to hold for other types.

A study, Hilleman ('55), was made in 1954 at an Army base in which evidence concerning infection wtih one of the above virus types (RI 67) was obtained on a large number of recruits. It was found that over 80% showed signs of having become infected during their first four months in the Army. Of these, only about 25% were hospitalized, indicating that many cases of ARD are subclinical and consequently not observed.

Table 1 presents the number of observed cases; *i. e.*, hospitalizations, by week, for the 117 flights observed. The pattern shown by the trend of weekly hospitalizations is typical of military recruit training centers with its peak at the fourth week and a rapid decrease beyond that peak. Three things are of particular interest: 1. There must have been some sort of immunity developing, because of the fall in number of cases after the fourth week. This decrease occurred in spite of a general and uniformly high level of incidence over the entire base during the period of the study. 2. There were many second and a few third cases, indicating that the immunity developed was not complete. 3. Apparently only a small proportion of the population was affected. There were 1,476 hospitalized out of 7,020 men. From observations made at the Army base mentioned above, it seems probable that there was a large amount of unapparent infection. These considerations formed the basis of attempts at constructing a model.

The distribution of the number of cases occurring in any one week, as shown in table 1, is interesting in itself. During the first week this distribution cannot be distinguished from a binomial. However, most

TABLE 1

Number of flights by number of first and number of repeat hospitalizations for ARD by week at Sampson AFB among 117 flights arriving between November 1, 1952 and March 1, 1953

No. of first hospitalizations	WEEK AT SAMPSON											
	1	2	3	4	5	6	7	8	9	10	11	12
0	94	42	16	12	22	56	78	97	99	111	103	97
1	18	30	30	16	27	30	29	14	14	6	13	15
2	5	24	19	22	24	15	9	3	2		1	4
3		10	15	14	17	9	1	1	2			1
4		6	12	17	11	3		1				
5		3	7	11	4	4						
6		1	6	10	4			1				
7		1	4	7	6							
8			4	3	2							
9			3	3								
10												
11				2								
over 11			1 *									
Total number	28	160	336	407	272	119	50	33	24	6	15	26
Mean per flt.	.24	1.37	2.87	3.48	2.32	1.02	.43	.28	.21	.05	.13	.22
Std. Dev.	.52	1.48	2.70	2.53	2.05	1.31	.67	.82	.30	.22	.36	.54
No. of repeat hospitalizations												
0	117	117	115	105	102	101	110	110	109	112	110	106
1			2	8	13	16	6	7	8	4	7	10
2				4	2		1			1		1
Total number			2	16	17	16	8	7	8	6	7	12
Mean per flt.			.017	.137	.145	.137	.068	.060	.068	.051	.060	.103

* In one flight 17 cases were observed in the third week.

of the following weeks show a variation much greater than would be expected from a binomial situation, which is in line with what one would expect from a process in which contagion exists.

Mathematical model

The primary purpose of this paper was to construct a model epidemic with properties which were compatible with the epidemic situation and observations. Consequently, a model was built with the following properties.

1. The probability of a highly susceptible man becoming infected from outside the flight in a small interval of time Δt is $\mu\Delta t + o(\Delta t)$, where μ is a constant. It follows that the probability α of a man escaping infection from outside in a unit period of time is $\alpha = e^{-\mu}$.

2. The probability of infection from within the flight in a small interval of time Δt is dependent upon I the number of infectious men within the flight. This probability is assumed to be $\lambda I\Delta t + o(\Delta t)$, and it follows that the probability of escaping such infection during a unit period of time, during which I is constant, is

$$\beta^I = e^{-\lambda I}.$$

3. Once recovered from infection, a man has partial immunity, and the constants μ and λ in 1 and 2 above are both altered by multiplying them by the same factor γ.

4. There exists a proportion, δ, of men who become infected but are not detected. These men remain in the group and provide the pool of infection from within.

5. Incubation periods are about 5 days.

6. Periods of infectiousness are unknown but are assumed to be less than 7 days.

In constructing a model based on these properties the 12 weeks of observation were considered separately. During each week the risks of infection were assumed to be constant, depending on the occurrences of the previous week. Remembering that only men placed in the hospital were observed, the following states were postulated. They account for the observations under the properties of the model.

State 1. Highly susceptible. No previous infection.

State 2. Moderately susceptible. One or more previous infections. Never hospitalized.

State 3. Moderately susceptible. At least one previous hospitalization. (Note: States 2 and 3 must be kept separate in order to identify men in States 8 and 9 below.)

State 4. Infectious. An unobserved case infected for the first time.

State 5. Infectious. An unobserved case infected at least once before. Never hospitalized.

State 6. Infectious. At least one previous hospitalization.

State 7. Hospitalized for the first time, no previous infection.

State 8. Hospitalized for the first time, one or more previous infections.

State 9. Hospitalized. At least one previous hospitalization.

The total number of men in States 7 and 8 were observed as first hospitalization. State 9 was observed as repeat hospitalizations. The remainder of the states were not observed but might have been under proper circumstances. Men in States 4, 5, and 6 provide the pool of infection from within the flight. This total is called I in property 1 above.

Some further assumptions were made. Actually a man can become infected at any time. In the model it was assumed that any changes occur at the close of each week. At that time infected men either enter the hospital or become and remain infectious and undetected. At the end of the following week they are well again and become moderately susceptible.

Table 2 presents the probabilities of changing from one state at time t to another state at time $t+1$. These are called transition probabilties. Justification for their choice follows. Suppose at time 0 all 60 men of the flight are well and highly susceptible (State 1). At the end of the first week the probability of a man remaining well (*i. e.*, of remaining in State 1) is the probability α of escaping infection from without.

$$\alpha = e^{-\mu},$$

where one week is the unit of time. The probability of becoming infectious and undetected (State 4) is $\delta(1-\alpha)$ and that of going to the hospital (State 7) is $(1-\delta)(1-\alpha)$, as implied by property 4.

Assuming that the close of the first week finds N_{11} men in State 1, N_{14} in State 4, and N_{17} in State 7, the probability of a man in State 1 remaining well during the second week is now

$$\alpha\beta^{I_1} = e^{-\mu}e^{-\lambda I_1}$$

where I_1 equals N_{14} which is the number of infectious men present at time $t=1$. The probability of going from State 1 to State 4 is now $\delta(1-\alpha\beta^{I_1})$, and that of going from State 1 to State 7 is $(1-\delta)(1-\alpha\beta^{I_1})$.

TABLE 2

Transition probabilities from time t to time $t+1$

TABLE 2

Transition probabilities from time t to time $t+1$

	STATE AT TIME t	STATE AT TIME $t+1$								
		SUSCEPTIBLE			INFECTIOUS			HOSPITALIZED		
		1	2	3	4	5	6	7	8	9
SUSCEPTIBLE	1 Highly susceptible (no previous case)	$\alpha\beta^{I_t}$	0	0	$\delta(1-\alpha\beta^{I_t})$	0	0	$(1-\delta)(1-\alpha\beta^{I_t})$	0	0
	2 Moderately susc. (no prev. hosp.)	0	$\alpha^{\gamma}\beta^{\gamma I_t}$	0	0	$\delta(1-\alpha^{\gamma}\beta^{\gamma I_t})$	0	0	$(1-\delta)(1-\alpha^{\gamma}\beta^{\gamma I_t})$	0
	3 Moderately susc. (one or more hosp.)	0	0	$\alpha^{\gamma}\beta^{\gamma I_t}$	0	0	$\delta(1-\alpha^{\gamma}\beta^{\gamma I_t})$	0	0	$(1-\delta)(1-\alpha^{\gamma}\beta^{\gamma I_t})$
INFECTIOUS	4 Infectious (no previous case)		1							
	5 Infectious (no prev. hosp.)		1							
	6 Infectious (one or more hosp.)			1						
HOSPITALIZED	7 Hospitalized (no previous case)			1						
	8 Hospitalized (prev. case but no prev. hosp.)			1						
	9 Hospitalized (one or more prev. hosp.)			1						

At the close of the second week the men in State 4 all enter State 2 and those in State 7 enter State 3 in accordance with the assumptions above.

Once infected and recovered (States 2 and 3) a man has partial immunity. In this situation the probability of remaining well during the $(t+1)^{\text{th}}$ week is

$$\alpha^{\gamma}\beta^{\gamma I_t} = e^{-\gamma\mu}e^{-\gamma\lambda I_t}$$

where γ is an index of immunity as given in property 3 above. A man in State 2 can remain there or go to States 5 or 8. A man in State 3 can remain there or go to States 6 or 9. All these transitions are summarized in table 2.

The parameters introduced above have fairly obvious meanings. The probability of escaping infection from outside is α. A contagion factor, β, is utilized once infections occur in a flight. Obviously, both α and β are between 0 and 1. $\beta = 0$ implies overwhelming contagion, and $\beta = 1$ implies no contagion. δ is the probability that, given a man is infected, he is not hospitalized. $\delta = 0$ corresponds to a situation in which everyone is isolated when infected. $\delta = 1$ means no infected people are isolated. In this model δ is assumed constant, regardless of the number of previous infections. γ is an immunity index. $\gamma = 0$ implies perfect immunity, $\gamma = 1$ means no immunity, and $\gamma > 1$ implies an increased susceptibility due to earlier infection.

Estimation of parameters

The problem of estimating the 4 parameters in this model is not simple and the project would have been abandoned without the presence of a CRC 102A electronic computer obtained from the National Cash Register Company. The method of choice in this estimation was maximum likelihood, but unfortunately the complexity of the model was such that the use of this method seemed impossible. Consequently, other (more questionable) means were adopted. A deterministic counterpart of the model was used to obtain expected values corresponding to the observations of first and repeat hospitalizations. Given values for α, β, γ, and δ, the transition probabilities were completely determined. Then, beginning with 60 men in State 1 in the first week, the expected numbers of men in States 1, 4, and 7 in the second week were computed. These in turn were used to get the various expected numbers for the third week. Thus for a given set of parameters which determined the transition probabilities, the deterministic counterpart could be computed

week by week. The computations were programmed for the electronic computer so that a complete deterministic epidemic for a flight of 60 men could be produced. The usual χ^2 goodness of fit expression was then used, not in the ordinary sense but merely as an index of the

TABLE 3

Number of flights by number of first and number of repeat hospitalizations by week of exposure of 415 Monte Carlo flights to a model of an epidemic of ARD

No. of first hospitalizations *	WEEK OF EXPOSURE											
	1	2	3	4	5	6	7	8	9	10	11	12
0	263	132	51	23	54	112	225	259	311	336	347	370
1	122	126	74	55	89	148	120	121	90	68	60	42
2	26	81	93	94	111	93	50	31	14	10	8	3
3	3	53	73	81	76	42	13	3				
4	1	17	47	76	48	15	6			1		
5		6	34	43	21	5		1				
6			20	26	12		1					
7			14	9	2							
8			6	3	1							
9			3	4	1							
10				1								
Total number	187	545	1130	1294	939	545	289	197	118	92	76	48
Mean per flt.	.45	1.31	2.72	3.12	2.26	1.31	.70	.48	.28	.22	.18	.12
Std. dev.	.67	1.24	2.00	1.84	1.60	1.15	.94	.70	.52	.59	.43	.34
No. of repeat hospitalizations †												
0	415	415	413	392	362	362	369	390	396	392	398	397
1			2	22	51	51	45	25	19	23	17	16
2				1	2	2	1					2
Total number			2	24	55	55	47	25	19	23	17	20
Mean per flt.			.005	.058	.133	.133	.113	.060	.046	.055	.041	.048

* Sum of numbers in states 7 and 8, see table 2.

† Number in state 9.

deviation of deterministic values from the observations. The computation of this index was also programmed for the computer and eventually a set of parameters could be inserted into the model, the deterministic results computed, the χ^2 index computed, and the index typed out on a flexowriter in two and a half minutes. This formed the

basic procedure for obtaining estimates of the four parameters, α, β, γ, and δ. A rapidly converging iterative process was found. Two parameters were guessed, and the other two were determined by trial and error to minimize χ^2. These two minimizing values were then fixed, and the first two parameters were varied to minimize the χ^2 once more. Six repetitions of this provided estimates accurate to three decimal places. Various guesses were tried as a starting point, all resulting in the same limiting estimates which were the following:

$$\alpha = .962 \qquad \gamma = .167$$
$$\beta = .941 \qquad \delta = .827.$$

The deterministic epidemic resulting from these estimates is given in table 4.

TABLE 4

Weekly incidence of hospitalizations for observed, Monte Carlo, and deterministic flights

	FIRST HOSPITALIZATION			REPEAT HOSPITALIZATION		
Week at Sampson AFB	117 observed flights	415 Monte Carlo flights(1)	Deterministic flights(2)	117 observed flights	415 Monte Carlo flights(1)*	Deterministic flights(2)†
1	28	53	46			
2	160	154	166			
3	336	319	368	2	1	1
4	407	365	418	16	7	6
5	272	265	243	17	16	17
6	119	154	121	16	16	18
7	50	81	70	8	13	13
8	33	56	44	7	7	10
9	24	33	31	8	5	7
10	6	26	24	6	6	6
11	15	21	20	7	5	5
12	26	14	18	12	6	5
All weeks	1476	1541	1569	99	82	88

* Incidence obtained for 415 flights multiplied by $\frac{117}{415}$.

† Deterministic mean multiplied by 117.

The value of χ^2 was approximately 72 when all 22 weekly observations of first and repeat hospitalizations were used in the fitting process. This was not a spectacularly good fit but as mentioned later the model certainly seems to have retained the features of the epidemic.

Monte Carlo epidemics

In accordance with the model as given in table 2, the transition probabilities depend on the parameters α, β, γ, and δ. Using the values obtained from the estimation just described, and assuming that 60 highly susceptible men begin in each flight, one can observe a "Monte Carlo flight" as it proceeds through 12 weeks of exposure. Such a flight was constructed by the following steps:

Step 1. First week. The computer generated 60 pseudo random numbers between zero and unity by a method analogous to those discussed in Cameron ('54), Juncosa ('53). Of these, the numbers which were less than α were taken to be men who remained well for the first week. Those between α and $\alpha + \delta(1 - \alpha)$ were men who received unapparent infections (these were put equal to I_1), while those greater than $\alpha + \delta(1 - \alpha)$ were men who were hospitalized. Suppose, for illustration, these groups had 57, 2, and 1 men in them, respectively.

Step 2. Second week. For the second week 57 random numbers were drawn, and those less than $\alpha\beta^{I_1}$, where $I_1 = 2$ in this example, remained well, those between $\alpha\beta^2$ and $\delta(1 - \alpha\beta^2)$ received unapparent infections, and those greater than $\delta(1 - \alpha\beta^2)$ were hospitalized. Now assume the observed numbers to be 52, 4, and 1, respectively.

Step 3. Third week. For the third week there were two men in State 2 and one in State 3 as a result of the first week's experience. Two random numbers were drawn and those less than $\alpha^\gamma\beta^{\gamma I_2}$, $(I_2 = 4)$, remained well in State 2 with the others being infected analogously to Step 2. Similarly, one random number was drawn yith the same disposition rule. The 52 remaining well men were handled as the 57 had been in Step 2.

Steps 4-12. Analogous to Step 3.

These steps were carried out for 12 weeks of exposure by the elec tronic computer. About 100 Monte Carlo flights could be exposed to the conditions of the model in 8 hours of machine time. A total of 415 flights were so exposed. Tables 3, 4, and 5 present some of the findings. Figure 1 is based on table 4. Comparing weekly hospitalizations for the observed and Monte Carlo flights by the χ^2 index gives a value of χ^2 equal to 98, somewhat larger than the value of 72 obtained by comparing the observed and deterministic results.

Table 3 presents the 415 Monte Carlo epidemics in a manner comparable with the presentation of the 117 epidemics in table 1. In table

TABLE 5

Percent of 117 observed flights and 415 Monte Carlo flights by number of hospitalizations for ARD during a 12 week period

NUMBER OF HOSPITALIZATIONS DURING 12 WEEK PERIOD (x)	PERCENT OF FLIGHTS WITH x HOSPITALIZATIONS AS FOUND IN 117 observed flights	415 Monte Carlo flights
0–4	1.7	.2
5–9	24.8	8.7
10–14	35.9	50.6
15–19	23.9	35.9
20–24	9.4	4.6
25–29	3.4	
30 and over	.9	
Mean *	13.5	13.8
Std. deviation *†	5.5	3.3

* Based on the data prior to grouping.

† There is a significant difference at the 0.01 level between the two standard deviations.

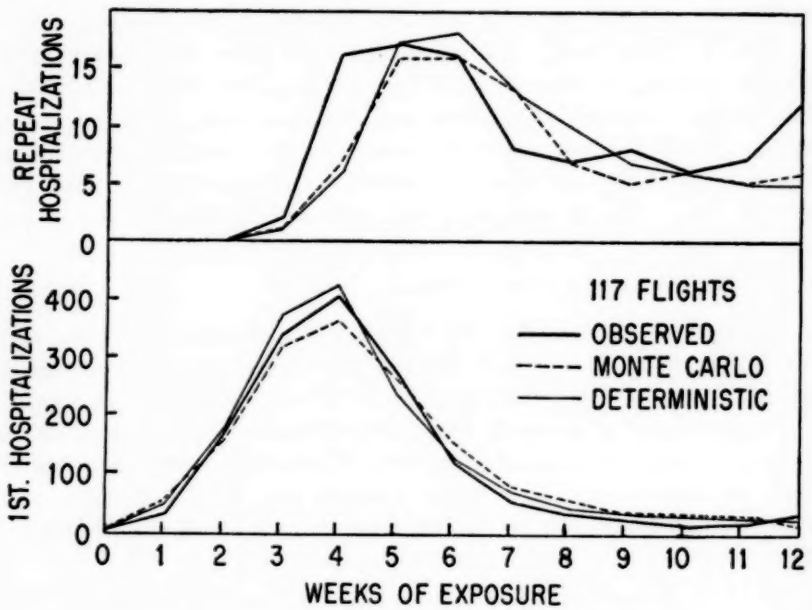

FIG. 1. WEEKLY INCIDENCE OF HOSPITALIZATIONS FOR 117 OBSERVED, MONTE CARLO, AND DETERMINISTIC FLIGHTS (See table 4 and its footnotes).

4 the weekly incidence of the observed, the Monte Carlo, and the deterministic epidemics are compared. Figure 1 presents these graphically. It appears that the model has come fairly close to the observations of first hospitalizations but that it cannot match the pecularities observed in repeat hospitalizations.

DISCUSSION

There are a number of questions associated with the epidemic model of this paper. First to be noticed is that this epidemic situation is a continuous process in time which has been forced to be a discrete one. Consequences of this are not clear, but are assumed to be slight. The incubation period of 3–5 days is shortened a bit in the model by assuming that men infected during one week are infectious during the following week. As a result of this assumption, the first week should show fewer observed cases than predicted by the model. This turned out to be true. The period of infectiousness for ARD is probably quite variable but the observations on volunteers mentioned earlier, Commission on Acute Respiratory Diseases ('47), indicate that the one week used in the model is a fairly reasonable estimate. The time a man is isolated in the hospital is assumed to be one week. This is probably too long, but unfortunately data were not available on this point.

More serious than the above is the fact that this model ignores men who were absent from the flight for reasons other than ARD. There was a lot of streptococcal disease and a sharp influenza outbreak during the period under study. Another difficulty is that men with extended absences were set back in their recruit training and transferred to other flights. Such transfers were not accounted for in this study. A third objection is that prior to being hospitalized infected men undoubtedly contributed to the risk of infection; however, the model ignores this.

The epidemic model of this paper, through its 4 parameters, has considerable versatility with respect to immunity, undetected cases, and contagion. Changing any of the parameters by as much as a few percent causes considerable change in the χ^2 index. The assumption that all men are equally prone to infection at time zero could have been modified in a simple manner by using a fifth parameter. However, the nearly binomial distribution observed for the first week lends credence to the equality of initial proneness which was assumed.

For simplicity, the model assumed that the risk of infection from without was constant. Examining hospitalization rates for the entirety

of Sampson Air Force Base reveals that this assumption was only approximately true, there being a lower risk in November and March than in the intervening months. This may account in part for the finding that the observed flights had greater variability in weekly incidence than did the Monte Carlo ones.

If the model were basically correct, the estimates of the 4 parameters would indicate something of the nature of the disease. Since $\delta = .827$, we would say there is indication that a large proportion, over 80%, of infections are subclinical. We would also say that $\gamma = .167$ implies that recovery from an infection results in partial immunity which increases the probability of escaping infection from outside the flight in one week from .962 to $(.962)^{.167}$ or .994. There is danger in attaching too much physical significance to the values of these parameters, however. There is always the possibility that the model used, while fitting the data, is not unique and is not a true representation of the underlying mechanisms.

The probabilistic theory of epidemics has long been concerned with the distribution of subjects in various states at a given time. Only rarely, however, are enough data available to observe these distributions empirically and to compare them with theoretical ones. The types of data used in this work are somewhat rare. Studies of families constitute the main effort in this direction. Of course similar information has long been collected at military installations, but never, to the author's knowledge, has it been published or studied from the viewpoint of this paper. It provides a means of checking theoretical models and, once the mathematical problems of estimation and distribution theory are solved, may lead in the future to far-reaching conclusions concerning the housing and treatment of susceptible populations.

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CHANGING TRENDS IN THE CHINESE-AMERICAN POPULATION

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CHINESE immigration to the United States won considerable publicity during the last 4 decades of the nineteenth century as the volume of immigration grew. In recent years, in contrast, the Chinese population has received relatively scant attention. This lack of interest attests to the changed role of the Chinese in the American economy. Briefly, because of the elimination of the Chinese from jobs desired by the whites, the Chinese question lost its economic significance and tolerant indifference took the place of hostility (McWilliams, '43).

Along with this altered economic role, other changes also occurred. Geographically, wider dispersion of the Chinese rapidly took place. The exclusion laws passed in 1882 and in subsequent years prevented additional substantial immigration. As a result, the Chinese suffered a consistent decline for several decades. Parallel with the decrease in numbers was a gradual increase in average age. The ability of the Chinese to survive was thus in doubt (U. S. Senate, '11).

With possibly only one exception (Thompson and Whelpton, '33), doubt as to the future of the Chinese population has persisted to the present. Lee ('47) predicted that "the Chinese population in this country is likely to decrease rather than increase." King ('50) expressed a similar, though less pessimistic, belief that "there would be some increase in the Chinese-American population in the next decade or so (1940-1950). Probably, however, no substantial increase or decrease will be observed."

In the present paper, this pessimistic opinion is assessed quantitatively in terms of the sex and age characteristics of the Chinese

population. Attention will be particularly focused upon more recent development insofar as the data permit.

In retrospect

The number of Chinese arrivals in the United States up to 1850 was variously estimated (cf. Coolidge, '09; Ferenczi, '29). According to one source, only 46 Chinese were recorded arriving in continental United States between 1820 and 1850. Of the 46, 31 were males and 15 females (Bromwell, 1856). The census of 1850 gave, without distinction of sex,

TABLE 1

Nativity of the Chinese population in the United States, by sex, 1850-1950

		Male			Female		
Year	Grand total	Total	Foreign born	American born	Total	Foreign born	American born
1950	117,140	76,725	40,469	36,256	40,415	14,581	25,834
1940	77,504	57,389	31,687	25,702	20,115	5,555	14,560
1930	74,954	59,902	39,109	20,693	15,152	4,977	10,175
1920	61,639	53,891	40,573	13,318	7,749	2,534	5,214
1910	71,531	66,856	54,935	11,921	4,675	1,661	3,014
1900	89,863	86,341	78,684	6,657	4,522	2,169	2,353
1890	107,488	103,620	*	*	3,838	*	*
1880	105,465	100,686	100,038	648	4,779	4,244	535
1870	63,199	58,633	58,325	308	4,566	4,357	209
1860	34,933	33,149	*	*	1,784	*	*
1850	758	*	*	*	*	*	*

Source: United States censuses. * No separate figures available.

a total of 758 Chinese in the country as a whole. Notwithstanding the discrepancies, the number of Chinese in this country could not have been very large in 1850.

Table 1 clearly reflects the great influx of Chinese in the 4 decades after 1850. The total number of Chinese would undoubtedly have been many times greater had not many of them returned home before their presence was recorded in the census.

Evident also in table 1 is the effect of the passage of the Exclusion Laws. With the greatly reduced immigration after 1882, the total number of Chinese dropped from 107,488 in 1890 to 61,639 in 1920. It was not without reason that the Immigration Commission in 1911 (U. S. Senate, '11) questioned the ability of the Chinese to survive.

However, as table 1 further suggests, the failure of the Commission to take into account the growing number of American-born Chinese in the population rendered its conclusions invalid.

The total number of Chinese rose to 117,140 in 1950. Except for 1930 and 1950 when increments in the number of foreign-born are also shown, this reversal of the previous trend of decline is attributable to the steady increase of American-born Chinese. Even during the period when the total number of Chinese was decreasing, the growth of the American-born was persistent. In 1870, some 20 years after the first sizable influx of immigrants, there were hardly more than 500 American-born Chinese, amounting to less than 1% of the total Chinese population. Three decades later in 1900 the number of American-born, having increased nearly 20 times, totaled 9,010 and constituted 10% of the Chinese population.

In 1940, the American-born group outnumbered the foreign-born for the first time in the history of the Chinese population in the United States. (There is some evidence indicating biased reporting of nativity among foreign-born Chinese. So the census figures concerning American-born Chinese must be accepted with reservation.) In spite of the post-World War II immigration, the American-born continued to outrank the foreign-born in numerical prominence and comprised 53% of the total Chinese population in 1950.

Changes in sex and age composition

The great influx of Chinese occurred, as previously noted, between 1850 and 1890. Setting aside socio-economic factors which both stimulated and retarded Chinese immigration to this country (cf. Coolidge, '09; Sandmeyer, '39), this tremendous increase evidently placed the Chinese, identifiable easily in terms of racial and cultural traits, in the limelight and fostered the growth of an impressionalistic fear of "invasion by immigration." But, the Chinese were much less feared for what is termed "phenomenal fecundity" (Thomas, '52) than were the Japanese in this country.

Entering this country some 40 years later than the Chinese, the Japanese population had a large number of females by 1920. In that year, there were in the Japanese population some 24,000 foreign-born females out of a population of 111,000; whereas, the Chinese population, totalling 60,000, had only 2,500 foreign-born females. There were also some 14,000 and 5,000 American-born females in the Japanese and Chinese populations, respectively, who were then below the reproductive

age. It was during this period that the charge of "phenomenal fecundity" was lodged against the Japanes (Strong, '34; Thomas, '52). Owing to a more tolerant attitude now, the Chinese probably will not be so stigmatized in the years to come, despite the growing number of females. Nevertheless, one of the reasons for which the Chinese were not feared for their "fecundity" in the 1920's and in the earlier years lay in the scarcity of females.

The number of females, as shown in table 1, has always lagged behind the number of males. In the 1860 census, a total of only 1,784 females was recorded; whereas, the number of males for that year was 33,149. In other words, there were 1,858.1 males per 100 females. From 1870 to 1910, the total number of females remained constantly under 5,000, while the number of males fluctuated violently. Thereafter, the males revealed a pattern of apparent stagnation, with a total of under 60,000 for three consecutive decades. During the same period from 1910 to 1940, the total number of females exhibited a trend of continuous growth, resulting in a more balanced sex distribution. The number of males per 100 females given in the census is as follows: 1,284.1, 1870; 2,106.8, 1880; 2,678, 1890; 1,887.2, 1900; 1,430, 1910; 695.5, 1920; 394.7, 1930; 285.3, 1940; and 189.6, 1950.

Foreign-born females were never more than a few thousand until 1950. American-born females, like American-born males, have increased steadily since the turn of the century. But, their numbers did not exceed 10,000 until 1930, and it was not until the end of the next decade that the total number of females reached 20,000, of whom 14,000 were American-born.

The scarcity of females, while reflecting the selectivity of migration in the decades prior to the adoption of the exclusion laws, was perpetuated by other immigration restrictions until recent years. Historically, therefore, the Chinese population was faced with the problem of replacement. As evident in the 1940 census, the total gain from 1930 amounted to only 2,600. Broken down by sex and nativity as shown in table 1, the over-all gain was the difference between the heavy loss of some 7,500 foreign-born males and the combined increase of 10,100 in the three remaining groups. Presumably, the mortality of the aging foreign-born male group, and possibly return migration to China, would more than likely have offset possible gains in the three other groups between 1940 and 1950.

Calculation of this sort, however, was upset by the relatively heavy immigration of Chinese after 1946. The gain of some 20,000 alien

Chinese not only served to bridge the gap of reproduction between the generations, but also helped to stabilize the age-sex structure of the Chinese population in the United States.

The consequences of the selectivity of, and the restrictions placed upon, the Chinese immigration in the nineteenth century are clearly shown in figure 1. The structure of 1900 consisted almost exclusively of males. Their age distribution, covering a wide range with a mode at 35–39 years of age, suggested a fairly old settlement. The age groups 15–19 and 20–24 were only a little larger than the age groups 60–64 and 65–69, reflecting the curtailment of immigration under the exclusion laws. The foundation of children was conspicuously small and, together with the barely visible female lateral, suggested the imbalance and instability of the population pyramid. The 1910 structure showed an enormous shrinkage of the male lateral from 1900. The female lateral remained about the same as a decade earlier. The pattern of instability persisted as the base of children was no larger than that of 1900.

The structures of 1920 and 1930 revealed the continuous contraction of the male lateral, notably in the age groups 45–49 and upwards. Certain other changes in the population pattern, however, also took place and were of significance. There appeared some expansion of the age groups 20–24 through 35–39 in both structures, reflecting the small amount of immigration in the two decades after 1910 (McEntire, '47). Evident also were the gradual growth of the female lateral and the enlargement of the base of children.

The development of a bimodal age distribution, for the males, was also suggested in the structures of 1920 and 1930. By 1940, the bimodal pattern of the males had sharpened, with the first mode at 15–19 years of age and the second mode at 40–44 years. For the females, owing to the selectivity of past immigration, a unimodal pattern persisted throughout the period up to and including 1940.

The 1940 structure again reflected the uninterrupted, but slow, expansion of the female lateral. Nevertheless, the foundation of children was smaller than in 1930, indicating a diminution in the rate of natural increase. While the aging of the first generation females and the immaturity of their American-born female descendants undoubtedly accounted for the decline, voluntary limitation of the family size was also responsible for the drop (Kowh, '47; McEntire, '47).

The structure of 1950 signified several far-reaching changes tending to balance and stabilize the Chinese population. While the bimodal pattern of the male persisted in 1950, their modes moved downward

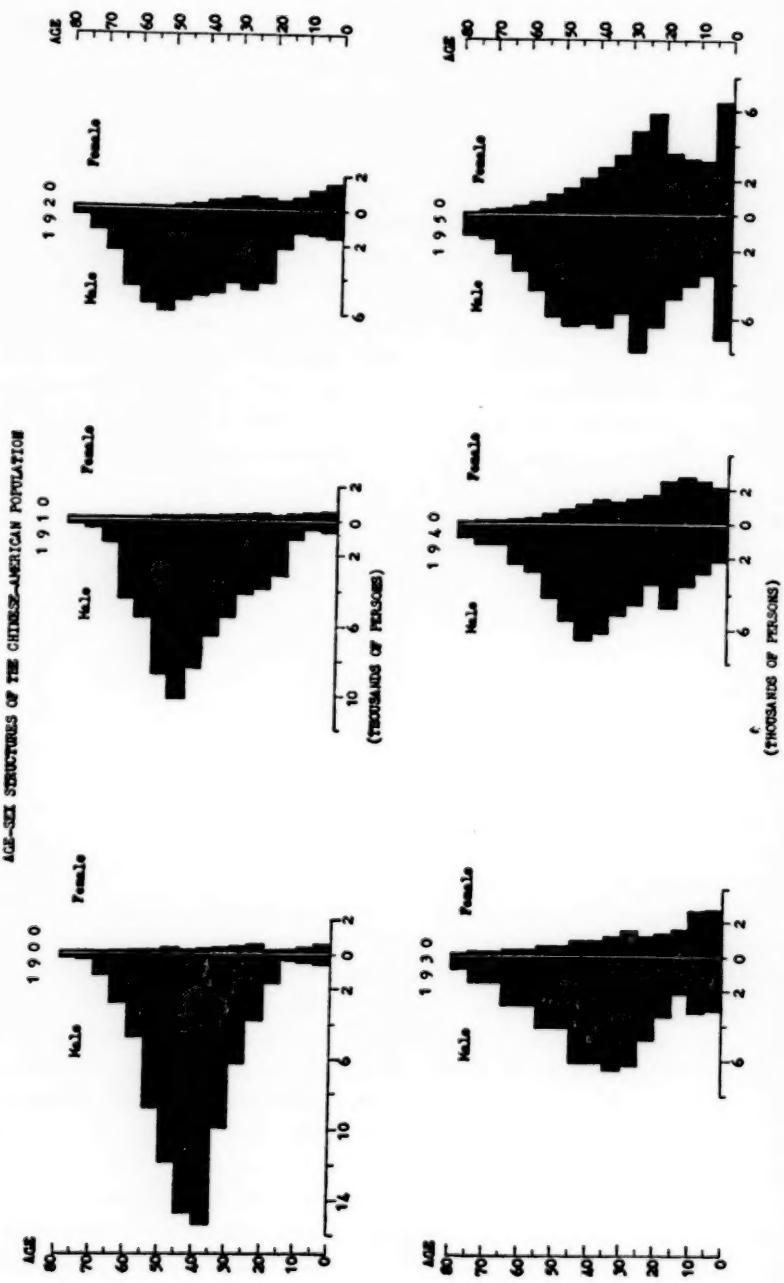
AGE-SEX STRUCTURES OF THE CHINESE-AMERICAN POPULATION
1900
1910
1920
1930
1940
1950
Male
Female
AGE
(THOUSANDS OF PERSONS)

FIG. 1.

from 1940; the first mode descended from 15–19 years to 0–4 years, and the second from 40–44 to 25–29.

For the females, there developed in 1950 for the first time a bimodal pattern of distribution, with the first mode within the same age group as for the males and the second mode at the age group 20–24. The inflow of brides and other immigrants inflated the female lateral, notably

TABLE 2

Births and deaths of the Chinese population, together with rates for the Japanese, 1940-1950 †

(*Rates per 1,000 estimated midyear population*)

Year	Birth			Death		
	Chinese		Japanese	Chinese		Japanese
	Number	Rate	Rate	Number	Rate	Rate
1950	5,139	43.9	24.5	*	*	*
1949	5,062	*	*	1,162	*	*
1948	4,210	48.4	23.2	1,162	13.4	6.7
1947	2,170	25.2	23.8	1,123	13.1	6.8
1946	1,534	18.5	21.5	1,279	15.8	7.0
1945	1,382	17.1	22.9	1,317	18.0	8.5
1944	1,291	16.3	22.9	1,324	17.9	7.6
1943	1,364	17.3	21.3	1,336	17.4	7.0
1942	1,220	15.6	17.3	1,206	15.7	7.4
1941	1,183	15.4	16.7	1,230	16.0	7.0
1940	1,098	14.1	14.7	1,184	15.2	6.7

Birth: For 1947-1950, based on population excluding armed forces overseas; for 1940-1946, on population including armed forces overseas.

Death: Exclusive of stillbirths and deaths among armed forces.

* Data not available.

† Source: *Vital Statistics—Special Reports*, U. S. Dept. of Health, Education and Welfare, PHS, National Office of Vital Statistics, Vols. 35, 36 and 37.

in the age groups 20–24 through 45–49, and significantly equilibrated the population pyramid. The foundation of children, having expanded considerably, represented the contribution of these females and a high rate of natural increase.

Table 2 gives the number of births and deaths of the Chinese from 1940 to 1950, inclusive, together with the rates for the Chinese and Japanese. These rates illustrate change in the two populations in recent years. After a decline in the rate of growth between 1930 and 1940,

the Japanese resumed their upward trend in the 1940 decade, reflecting the coming of age of their American-born females. The 1950 census gave indication of only very small Japanese immigration since the end of World War II. The growth of the Japanese population in the 1940 decade therefore could not have been due to an increase of foreign-born females in the reproductive period.

As previously indicated, the Chinese population should have declined or remained stationary in the 1940 decade. Their birth and death rates between 1940 and 1945 unequivocally confirmed the correctness of the prediction. Beginning in 1946, however, the admission of Chinese females brought about the most startling change in the rate of natural growth: the birth rate for 1950 was nearly three times greater than the rate for 1940. The high birth rate of more than 40 per 1,000 is significant, particularly in view of the high sex-ratio of the Chinese which was 189.6 in 1950.

Although the crude death rate of the Chinese showed an apparent decline after 1945, it is very doubtful that the decline owed much to improved mortality conditions. While the number of deaths remained nearly the same during all the years of the 1940 decade, the decline in rate was obviously caused by the shifts of the population base upon which these rates were calculated.

In any event, from 1946 onward, the birth rate of the Chinese has far surpassed the death rate, and the number of births was far above replacement needs. With the majority of the foreign-born females still in the reproductive period and the coming of age of American-born females, the growth of the population in the next several decades can be certain if the mortality of the Chinese remains the same, or even shows some increase.

SUMMARY

The Chinese population was highly unstable and imbalanced at the beginning of the century. During the last 50 years, in spite of adverse demographic conditions, their numbers gradually increased. The rate of natural increase, however, did not contribute to the maintenance of the population size until after 1920. While the population grew in the two decades prior to 1940, it was believed that the Chinese population should have declined or remained stationary in the 1940 decade. The birth and death rates of the Chinese from 1940 to 1945 supported this view. But, the post-World War II immigration not only tended to balance the sex ratio of the Chinese, but also bridged the gap of reproduction between

the generations. Consequently, a considerable increase of the Chinese was recorded in 1950. While it seems certain that the Chinese, with the passage of time, will exhibit the pattern of controlled fertility, there is no reason to assume that their numbers will not increase in the near future. The 1950 population of the Chinese contained the largest number of females and children ever known in the entire history of the population in this country. With the majority of foreign-born females still in the reproductive period and the coming of age of American-born females, a further growth in absolute numbers of the Chinese seems assured for at least several decades.

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VARIATIONS WITHIN INDIVIDUALS IN HUMAN BIOLOGY

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WHEN anatomical or physiological measurements are taken repeatedly on a single subject, the results obtained on different occasions will not usually agree exactly, even when conditions are carefully standardized. Discrepancies will result from actual errors of measurement, and these may be superimposed on real fluctuations in the quantity measured. In this article, both sources of variation will be referred to as *errors*. When real fluctuations are present, this terminology carries the implication that the subject possesses a *stable value*, about which random variations occur. For simplicity I leave aside the case in which the "stable" values actually change slowly with time; this can often be allowed for by a fairly simple extension of the analysis discussed here.

The assessment of errors

When some measuring technique is proposed, it is desirable to give some idea of its precision. Equally, in considering some physiological measurement it is of interest to know the extent to which this measurement fluctuates from time to time. Both questions can be included in the same investigation, but to simplify the discussion I shall consider only one aspect of the problem—either we are measuring a quantity which does not change with time (such as many anatomical measurements on adults) or we are investigating a variable quantity with instruments whose errors (at least with a single observer) can be ignored.

For an investigation of this kind we require that repeated measurements shall be taken by several observers on each of a number of subjects. It is important that the observers should form a representative sample

of all possible observers, but the subjects may be chosen to give an even coverage of the whole range of measurements. In practice it is neither necessary nor desirable to have more than two measurements by each observer on each subject. It is assumed that the errors are equally variable at all points of the scale (a transformation of the scale of measurement may be necessary for this purpose); apart from statistical simplicity, this also makes the presentation of the results more straightforward. If necessary, the total number of measurements taken can be reduced by refinements in the experimental design, but this type of complication can easily be allowed for. In the simplest case, then, with p subjects and q observers, we can work out an analysis of variance as shown in table 1.

TABLE 1

	D. F	MEAN SQUARES	EXPECTED MEAN SQUARES
Subjects	$p-1$	V_S	
Observers	$q-1$	V_O	$2p\sigma^2_O+2\sigma^2_{SO}+\sigma^2_D$
Subjects $\times$ Observers	$(p-1)(q-1)$	V_{SO}	$2\sigma^2_{SO}+\sigma^2_D$
Duplicates	pq	V_D	σ^2_D

This in turn implies a model for the observations of the form

$$y = y_S + \epsilon_O + \epsilon_{SO} + \epsilon_D$$

y is the observed reading and y_S the stable value for the subject concerned, while the ϵ's relate to the particular observer, the particular observer-subject combination and the particular observation respectively. We assume further that the ϵ's are random variables, independently distributed with variances σ^2_O, σ^2_{SO} and σ^2_D. Then the expected values of the different mean squares are those shown in the last column of table 1.

The interpretation of the constants is quite straightforward. ϵ_D represents the error of measurement in the narrowest sense. ϵ_O, constant for a particular observer, allows for a constant personal bias. ϵ_{SO}, the interaction constant, is a little less familiar; it allows for the fact that an observer's bias may in practice vary from one subject to another. The assumption of independence is of some importance. It implies that the subject $\times$ observer interaction is not systematic—it is not the

case, for example, that some observers always tend to over-estimate large measurements and under-estimate small measurements relative to others.

Estimates of the variance components are readily obtained from table 1. We have

$$s^2_D = V_D$$
$$s^2_{SO} = (V_{SO} - V_D)/2$$
$$s^2_O = (V_O - V_{SO})/2p.$$

If a single observer takes two measurements on the same subject, the difference between them is simply $\epsilon_{D1} - \epsilon_{D2}$; the standard deviation of such differences is therefore estimated by $\sqrt{2}s_D$. If two different observers are involved, however, the difference involves the ϵ_O's and ϵ_{SO}'s, and the standard deviation is estimated by $\sqrt{[2(s^2_O + s^2_{SO} + s^2_D)]}$.

Methods of reporting measuring errors

A variety of ways of reporting measuring errors can be found in the literature. Most authors have considered the case of a single observer. With duplicate measurements on p subjects we can simply form the p differences and calculate s^2_D as the (crude) sum of squares of the differences divided by p. This quantity is often referred to as s^2_{meas}. A more roundabout way of calculation that has been quite widely used is to find the correlation coefficient between the two sets of readings. Denoting the population value by ρ, several authors give the formula

$$\sigma^2_{\text{meas}} = \sigma^2(1 - \rho)$$

where σ^2 is the average variance of the two sets of readings. For this to be true, ρ must be the intra-class correlation (Fisher, '54), a qualification that is often overlooked. With duplicate readings, the much simpler difference technique is available; with more replicates, ρ is most easily calculated from the analysis of variance table, so that this method has little to recommend it.

ρ is commonly referred to as the "reliability coefficient" and there is some case for reporting a correct estimate of it when the accuracies of different measurements are being compared. For this purpose, it is essential to use a representative sample of subjects, since the estimate of σ^2 involves an estimate of the variance of the population of subjects. In general, however, estimates of the variance components are likely to be more useful.

The precision of variance components

It may be necessary to get some idea of the precision with which the various σ^2's have been estimated. The theory for calculating fiducial intervals for variance components was given by Fisher ('35), but the necessary tables have not been calculated. A usable approximation has been worked out by Bross ('50). Consider the estimate $s^2_o = (V_o - V_{so})/2p$. We calculate the variance ratio $F = V_o/V_{so}$ with $(q-1)$ and $(p-1)(q-1)$ degrees of freedom and obtain four values of F from tables (5% tables will give 90% fiducial limits). These are

F_o with $(q-1)$ and $(p-1)(q-1)$ d. f.
F'_o with $(q-1)$ and ∞ d. f.
F_1 with $(p-1)(q-1)$ and $(q-1)$ d. f.
F'_1 with $(p-1)(q-1)$ and ∞ d. f.

Then the lower limit is given by

$$(V_o - F_o V_{so}) s^2_o / (F'_o V_o - F_o V_{so})$$

and the upper limit by

$$(V_o - V_{so}/F_1) s^2_o / (V_o/F'_1 - V_{so}/F_1).$$

If the observed value of F is less than F_o the lower limit becomes negative and must be replaced by zero. In this case Tukey ('51) gives a better approximation to the upper limit as

$$(V_o - V_{so}/F_1) s^2_o / (V_o/F'_1 - V_{so}/F'_1)$$

which is most easily calculated as

$$(V_o - V_{so}/F_1) F'_1/2p.$$

The effects of variation within subjects on regression and correlation coefficient

We now pass to the case where two different measurements are taken on each subject and interest centers on the relations between the measurements rather than on the variability as such. For this type of investigation it is necessary that the subjects should form a properly constituted sample, in which case we can define the variance of their stable values, σ^2_s, and estimate it from table 1 as $(V_s - V_{so})/2q$. For simplicity, we consider the case of a single observer and duplicate readings on each measurement.

We now can construct an analysis of covariance as shown in table 2, denoting the two measurements by x and y

TABLE 2

		Mean Squares and Products		
	d. f.	x^2	xy	y^2
Subjects	$p-1$	A	C	E
Duplicates	p	B	D	F

We can estimate the variances of the stable values of x and y by $V_{xx}=\frac{1}{2}(A-B)$ and $V_{yy}=\frac{1}{2}(E-F)$ respectively, and in the same way their covariance by $V_{xy}=\frac{1}{2}(C-D)$. Then the regression coefficient of y on x (stable values) is estimated by V_{xy}/V_{xx}, that of x on y by V_{xy}/V_{yy} and the correlation coefficient by $V_{xy}/\sqrt{(V_{xx}V_{yy})}$. The effect of the errors on these coefficients should be noted. The estimate of the regression coefficient of y on x, calculated from a single series of observed values would be $(C+D)/(A+B)$. Now the errors will often be almost uncorrelated, so that D will be small, whereas B, being a variance, is essentially positive; consequently the regression coefficient is usually reduced in magnitude by the presence of errors in the independent variate. This is true of both regression coefficients and consequently of the correlation coefficient also.

This reduction in the size of the coefficients is fairly well known under the name of "attenuation," and various correction formulae, assuming uncorrelated errors, have been given. Yates ('53), for example, gives the corrected regression coefficient as the crude coefficient divided by $(1-h)$ where h is the ratio of the error variance to the total variance in the independent variate. Spearman's formula gives the corrected correlation as the crude coefficient divided by the product of the reliability coefficients. Both these formulae differ from our result only in terms of order $1/p$ that are quite negligible with the number of subjects usually encountered.

The precision of regression coefficients

When a regression coefficient has been calculated in the above way, some idea of its precision will often be needed. This and allied topics have been discussed in an important paper by Tukey ('51).

We may start with a slightly different problem. If the estimated

correlation coefficient between the stable values is close to unity, it may be suggested that the stable values are *exactly* linearly related, the observed scatter being entirely done to the errors. Even when such a suggestion is implausible biologically, it may serve as a useful means of summarizing a set of results. The problem of determining the line of best fit has been discussed by statisticians and biologists, notably in connection with the allometric relationship; Tukey's approach appears to give a very satisfactory solution to a form of the problem that often arises in practice.

Suppose then that the true values lie on a line whose equation is $y - \mu x = c$; then any discrepancies between the observed values of $y - \mu x$ for the different subjects must be due to error. Now we do not know the value of μ; but we can replace it by a symbol m and work out an analysis of variance of $(y - mx)$ in the usual way. Values of m which give a non-significant variance ratio at a predetermined level of probability then define a fiducial range for μ; if no such real values exist, the data significantly contradict the hypothesis of strict linearity at the chosen probability level. When a point estimate of μ is required, this approach makes it natural to take the value of m which makes the variance ratio a minimum. This value is one root of a quadratic equation which is most easily written in the form of a determinant

$$\begin{vmatrix} 1 & m & m^2 \\ A & C & E \\ B & D & F \end{vmatrix} = 0.$$

The fiducial limits are the roots (if real) of the equation

$$\frac{\mu^2 A - 2\mu C + E}{\mu^2 B - 2\mu D + F} = \Phi$$

where Φ is the significance point of the F-distribution with $p - 1$ and p d.f.

Returning to the estimation of the regression of the stable values of y on x, only approximate results are available. Tukey ('51) gives a formula for the variance of the regression coefficient, but this is not altogether satisfactory—for one thing, it does not give the correct answer in the absence of errors—and I suggest as an alternative

$$\mathrm{Var}(b) = \frac{\dfrac{A}{p-1}\left(E - \dfrac{(C-D)^2}{A-B}\right) + \dfrac{BF}{p}}{(A-B)^2}.$$

Numerical example

As an example of some of the methods discussed above, I use readings of oral and rectal temperatures taken on two occasions about a week apart on 46 young men (Tanner, '51). The "errors" here are mostly physiological fluctuations, the errors of measurement being comparatively small. The analysis of covariance gives the mean square and products shown in table 3.

TABLE 3

	d. f.	Oral (°F) x^2	xy	Rectal (°F) y^2
Subjects	45	0.31119	+0.25443	0.29209
Duplicates	46	0.04685	+0.03424	0.07489
Stable values		0.1322	+0.1101	0.1086

Considering first the variates separately, the "errors" in oral temperatures are distributed with a standard deviation estimated by $\sqrt{(0.04685)} = 0.216°$. This means that two readings of oral temperature taken on the same subject at a weekly interval should not differ by more than $1.96 \times \sqrt{2} \times 0.216 = 0.60°$ in 95% of all cases. Put another way, a single reading of oral temperature can be expected to fall within $\pm 0.42°$ of the stable value 95% of the time.

The stable values are distributed with variances and covariance whose estimates are given in the last line of table 3—here, for example, $0.1322 = \frac{1}{2}(0.31119 - 0.04685)$. The mean of all the oral temperatures was 98.08° so that we expect 95% of the population to have stable oral temperatures in the range $98.08 \pm 1.96\sqrt{(0.1322)} = 97.37°$ to 98.79°. The variance of a set of single readings is estimated as $0.1322 + 0.0468 = 0.1790$, giving a standard deviation of 0.42°.

To set limits on the variances of the stable values, we find from tables of $2\frac{1}{2}\%$ significance points

$$F_0 = 1.80 = F_1$$

$$F_1 = 1.45 = F_1$$

so that for oral temperatures we have the lower limit

$$\frac{0.31119 - 0.04685 \times 1.80}{0.31119 \times 1.45 - 0.04685 \times 1.80} \times 0.1322 = 0.0817$$

and the upper limit

$$\frac{0.31119 - 0.04685/1.80}{0.31119/1.45 - 0.04685/1.80} \times 0.1322 = 0.1998$$

Tukey's modification gives an upper limit of 0.2067.

Turning to the relationship between the two variates we have for the stable values

regression coefficient of y on $x = +0.1101/0.1322 = +0.833$

regression coefficient of x on $y = +0.1101/0.1086 = +1.014$

correlation coefficient $= +0.1101/\sqrt{(0.1322 \times 0.1086)}$

$= +0.919.$

These may be compared with the "attenuated" values that would have been obtained from a series of single measurements, $+0.806$, $+0.786$ and $+0.796$ respectively.

If we wish to estimate a strict linear relationship of the form $y - \mu x = c$, we estimate μ from the equation

$$\begin{vmatrix} 1 & m & m^2 \\ 0.31119 & 0.25443 & 0.29209 \\ 0.04685 & 0.03424 & 0.07489 \end{vmatrix} = 0.$$

This gives $0.009053 - 0.009621m - 0.001265m^2 = 0$, and the appropriate root is $m = +0.8466$. With this value, the analysis of variance for $y - mx$ is

	d. f.	*MS*	*F*
Subjects	45	0.08433	1.670
Duplicates	46	0.05049	

The variance ratio lie just beyond the 5% level of significance. For illustrative purposes, I calculate the 1% fiducial limits. These are the solutions of

$$\frac{0.31119m^2 - 0.50886m + 0.29209}{0.04685m^2 - 0.06848m + 0.07489} = 2.01$$

or

$$0.21702m^2 - 0.37122m + 0.14156 = 0$$

giving $m = 0.574$ to 1.137.

Returning to the regression of y on x, the estimated coefficient is 0.833. The variance of this quantity is approximately estimated as

$$\frac{\frac{0.31119}{45}\left(0.29209 - \frac{0.22019^2}{0.26434}\right) + \frac{0.04685 \times 0.07489}{46}}{(0.26434)^2} = 0.01185,$$

giving a standard error of ± 0.109.

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CONTRIBUTION TO THE STUDY OF THE QUESTION OF ASSOCIATION BETWEEN TWO DISEASES *

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1. INTRODUCTION

THIS paper deals with some questions on the association between two diseases: how to define this concept and how to assess it. These considerations found their origin in the Research Seminar on Statistical Problems of Health, directed by Dr. J. Neyman, held at the Department of Statistics, University of California, Berkeley, during the summer of 1956. The subject of this paper was inspired by the Pearl-Wilson problem of the association between cancer and tuberculosis, Pearl ('29), Wilson ('30), Wilson and Maher ('32). However, the discussion applies equally well to any pair of diseases, so that for the sake of generality we shall denote these two diseases by A and B. The main part of the paper is concerned with a discussion of various possible definitions of association, their inter-relation, and their evaluation. In the Appendix a method is presented for dealing mathematically with the relevant stochastic models.

2. DEFINITIONS OF ASSOCIATION BASED ON FUNDAMENTAL PROBABILITY SETS

There is more than one way in which the concepts independence, positive association and negative association between diseases A and B can be defined, and it is therefore quite important to be clear about which definition one should adopt. First of all one can focus attention

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on a certain well-defined group of individuals and sort this group into 4 categories, denoted, respectively, by O, A, B and AB: those individuals who have neither A nor B, those who have A only, those who have B only, and those who have both. Let the numbers of indiivduals in these categories be n_O, n_A, n_B and n_{AB} and define the ratio R_1 as

$$R_1 = \frac{n_O n_{AB}}{n_A n_B} . \tag{1}$$

Any such group of individuals on which the ratio R_1 is based is sometimes called a "Universe of Discourse" Wilson ('30), sometimes a "Fundamental Probability Set," Neyman ('50), abbreviated FPS. We shall adopt the latter nomenclature. In whatever FPS we have adopted, the diseases A and B are said to be positively associated if $R_1 > 1$, independent if $R_1 = 1$ and negatively associated if $R_1 < 1$. An equivalent definition can be give nin terms of the ratio

$$R'_1 = \frac{n n_{AB}}{n'_A n'_B}$$

in which $n = n_O + n_A + n_B + n_{AB}$ is the total number of individuals in the FPS, $n'_A = n_A + n_{AB}$ is the number of individuals having disease A, and $n_B = n'_B + n_{AB}$ is the number having B. The two ratios R_1 and R'_1 are either both > 1, or both $= 1$ or both < 1, so that the definition of association using R'_1 coincides with the definition using R_1.

Examples of the above definition may be found in the papers by Pearl ('29), Wilson ('30) and Wilson and Maher ('32). The FPS considered by Pearl consisted of all individuals who had died in a certain hospital during a certain period, and the classification into the 4 categories was done by determining at autopsy the presence or absence of A or B. Pearl found that with respect to this particular FPS cancer and active lung T. B. are negatively associated and suspected that this result has various practical implications. These findings were criticized by Wilson who showed that one can define more than one FPS, compute R_1 (or R'_1) for each of them and arrive at contradictory conclusions. Thus, he first took the FPS composed of all individuals who had died in the United States during a certain year and sorted them into the 4 categories. In this population the ratio R_1 showed that A and B were negatively associated, as in Pearl's case. Next Wilson took the FPS of all individuals who were alive at some time during the year under consideration. Those who died by the end of the year were sorted as before; those who were still alive (*i. e.*, the great majority)

were classified as having neither A nor B. In this FPS the ratio R_1 showed positive association. Since the two procedures lead to opposite conclusions, Wilson puts the question as to which one is correct.

At this point it may be remarked that one may have some objection to Wilson's second procedure for the following reason. Whatever definition one wants to adopt for the association between diseases A and B, it should not depend on the period of observation T. In Wilson's examples this period was $T=1$ year, but it could equally well have been, say, half year or two years. Now in equation (1) the quantities n_A, n_B and n_{AB} represent the numbers of individuals in the various categories, having died during the period T, so that these quantities are approximately proportional to T. On the other hand, in Wilson's second example n_O is practically equal to the size of the live population, and is therefore approximately independent of T. Hence, by this procedure R_1 would be approximately inversely proportional to T. In other words, observations over a short period would make one believe that A and B are positively associated, whereas observations over a long period would lead to the conclusion that A and B are negatively associated. Obviously, this is not a satisfactory procedure. However, Wilson himself considers still further procedures to define association, all of them considering the individuals alive with either disease. The procedure most favored by Wilson is to abandon basing the definition of association on mortality data altogether, and instead, base it on morbidity data alone. This means that the FPS to be adopted should consist solely of the individuals alive at a certain time and should be sorted into the 4 categories O, A, B, AB. Association is then defined, as usual, in terms of the ratio R_1, computed from (1). It will be seen in section 4 that the ratio R_1, so computed, is the empirical determination of the ratio R_2, given by (8), or of its probabilistic analogues given by the left-hand sides of (12) and (14). For a discussion of the value of these ratios we refer to section 5.

3. DEFINITIONS OF ASSOCIATION BASED ON MATHEMATICAL MODELS

It cannot be denied that the evaluation of various percentages relating to certain classes of individuals in the general population does present some interest. In particular, Pearl's finding of a negative association between cancer and tuberculosis among the deceased is certainly interesting. However, similar studies acquire a particular interest and, occasionally, practical importance if they are not performed for their

own sake but as a means for finding something about the mechanism behind a phenomenon. In the particular case of discussion between Pearl and Wilson, the relevant phenomenon that both authors had undoubtedly in mind is the phenomenon of acquiring either cancer or tuberculosis, or both, and eventually succumbing to them. Thus, one of the most relevant questions is whether the contracting of a disease A by an originally healthy person increases, decreases, or leaves unchanged his chances of contracting also the disease B. The same question can be asked with A and B interchanged. Finally, the question arises whether the risk of death of a person having both A and B is different from what would be expected on the basis of the death risks from A and B separately. The following pages are written with these particular questions in mind. It will be noticed that these questions are related to the contrasting concepts of prevalence and incidence of diseases that are the subjects of current discussions by a number of authors, such as Dorn ('51), Sartwell and Merrell ('52) and Neyman ('55).

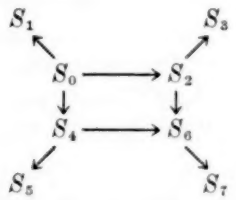

FIG. 1. DIAGRAM UNDERLYING THE SIMPLEST MATHEMATICAL MODEL TO REPRESENT THE PHENOMENON OF ACQUIRING DISEASES A AND B AND SUCCUMBING TO THEM.

The method of approach to the problem of association between the diseases A and B, as presented in this and the following sections, requires the construction of a mathematical model of the phenomenon of acquiring the diseases in question and of succumbing to them. An example of such a model can be found in the treatment of recovery, relapse, death and loss of patients by Fix and Neyman ('51). The model represented by the diagram in figure 1, proposed by Dr. J. Neyman, is one of the simplest models relevant to the question of association between diseases A and B. We postulate that at any time (t) each individual of the population under consideration must be in one of the following exclusive states:

S_0 = state of being alive without A and without B.

S_2 = state of being alive with A but without B.

S_4 = state of being alive without A but with B.
S_6 = state of being alive with both A and B.
S_1 = state of being dead, having been in S_0 just prior to death.
S_3 = state of being dead, having been in S_2 just prior to death.
S_5 = state of being dead, having been in S_4 just prior to death.
S_7 = state of being dead, having been in S_6 just prior to death.

As time goes on, an individual, originally in a particular state S_i, may transfer to another state S_j. Also, certain states (those of being dead) are "terminal," or "absorbing," and no transitions from them are possible. The detailed assumptions regarding the transitions from one state to another constitute the model. In relation to the problem of association between the two diseaeses A and B, the simplest assumptions regarding the transitions are indicated by arrows in figure 1. It will be seen that in this model no transition is reversible, *i. e.*, if an individual leaves a state S_i, then no return to this state is possible. This implies that each of the diseases A and B is so dangerous as to preclude recovery.

The diagram of figure 1 will first be used as the basis for a deterministic model. Instead of considering the number of individuals in the various states, we shall think of a substance present in and flowing between the various states. At a certain fixed time let the amount of substance in state S_i be x_i $(i = 0, 2, 4, 6)$ and let the amount flowing from S_i to S_j per unit time be proportional to x_i, with proportionality constant q_{ij}. The product $x_i q_{ij}$ represents then the flow per unit time from S_i to S_j. The model is completely determined by specifying the values of the flow intensities q_{ij}. It should be noted that several q_{ij} are equal to zero, namely, those not corresponding to an arrow in figure 1. For convenience of terminology we shall call q_{02}, q_{04}, q_{26}, q_{46}: *incidence intensities*, and q_{01}, q_{23}, q_{45}, q_{67}: *mortality intensities*.

It is possible now to define association between diseases A and B in terms of assertions on the values of the q_{ij}. In fact, there are two concepts which have to be distinguished: association between incidence of A and B, and association between mortality from A and B. This leads to three definitions, given below.

DEFINITION 1. We shall call A and B *incidence-independent* if

$$q_{02} = q_{46} \text{ and } q_{04} = q_{26}. \tag{2}$$

Positive and negative incidence association can be defined by replacing

the equalities in (2) by the appropriate inequalities. The interpretation of (2) is that if A and B are incidence-independent, then the risk of acquiring B is independent of whether or not A is present; and the same statement with A and B interchanged.

Before defining mortality-independence we shall make the assumption that an individual possessing a certain disease has, in addition to the risk of dying from this disease, independently a risk of dying from other causes, and we assume, moreover, that the latter risk is equal to that of a healthy person. These assumptions are expressed in the following analysis of q_{23}, q_{45} and q_{67}

$$
\begin{aligned}
q_{23} &= q_{01} + q'_{23} \\
q_{45} &= q_{01} + q'_{45} \\
q_{67} &= q_{01} + q'_{67}
\end{aligned} \tag{3}
$$

in which q'_{23}, q'_{45} and q'_{67} correspond to the risk of dying from A alone, B alone, or AB respectively.

DEFINITION 2. We shall call A and B *mortality-independent* if

$$q'_{67} = q'_{23} + q'_{45} \tag{4}$$

expressing the additivity of the risk intensities of the two independent causes of death.

DEFINITION 3. A and B will be called *completely independent* if they are both incidence- and mortality-independent.

The diagram in figure 1 will now be used for a stochastic model. At time $t = 0$ (birth) an individual starts in state S_0 and in the course of time he may make transitions to other states along the arrows indicated in figure 1. The time t is identified with the age of the individual. The transition intensities will be denoted again by q_{ij}.[1] We shall assume the same analysis, given by (3), of q_{23}, q_{45} and q_{67}. Unlike in our deterministic model, the q_{ij} will in general not be constants, but depend on the age t. In addition q'_{23} and q_{26} may also depend on how long the person has had disease A. Similar remarks apply to q'_{45}, q_{46} and q'_{67}. In other words, some of the q's may be both age dependent and duration dependent (the duration referring to the disease or diseases). Mathematically this is conveniently handled as follows.

[1] The exact meaning of the transition intensity q_{ij} is as follows: For a small interval of time Δt, the conditional probability that an individual in state S_i at time t will be transferred into S_j before the moment $t + \Delta t$, is given by $q_{ij}\Delta t + o(\Delta t)$.

If disease A is contracted, let u be the time at which this happens. Similarly, if B is contracted, let v be the time at which this happens. It is, of course, possible that both events happen in succession, which has the result that the individual enters S_6. Then, in general, q'_{23} and q_{26} are functions of t and u, q'_{45} and q_{46} of t and v, and q'_{67} of t, u and v. On the other hand, q_{01}, q_{02} and q_{04} will be only functions of t. Incidence- and mortality-independence will be defined by equations analogous to (2) and (4). Thus, we have as definition of incidence-independence

$$(2') \qquad q_{02}(t) = q_{46}(t, v), \qquad q_{04}(t) = q_{26}(t, u)$$

identically in t, u, v, and as definition of mortality-independence

$$(4') \qquad q'_{67}(t, u, v) = q'_{23}(t, u) + q'_{45}(t, v)$$

identically in t, u, v.

As was said before, the model based on the diagram of figure 1 does not allow recovery from either A or B. A more general model is based on the diagram presented in figure 2. The diagram is understood to

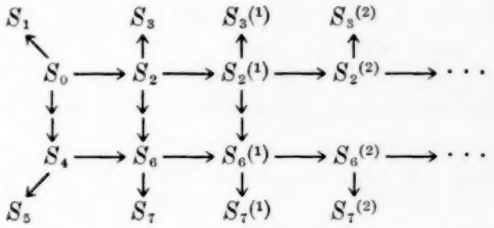

FIG. 2. EXTENSION OF THE DIAGRAM IN FIGURE 1 TO ALLOW FOR A RECOVERY-RELAPSE SEQUENCE IN DISEASE A.

extend indefinitely to the right. The meaning of the states $S_1, \cdots, S_7$ is as before. $S_2^{(1)}$ can be taken either as a state of being recovered from disease A, or as a state of having A in an inactive form (as in tuberculosis). $S_2^{(2)}$ is a state of relapse into the active form of A, etc. The states S_6, $S_6^{(1)}$, etc. have the same meaning as the corresponding states S_2, $S_2^{(1)}$, etc., with the additional specification that disease B is also present. The states labeled with an odd subscript denote again the corresponding state of being dead. The model could be extended to allow for a similar recovery-relapse sequence in patients with disease B, but this will not be done here. The diagram in figure 2 can be used either for a deterministic or for a stochastic model. In either case,

the association between A and B can be defined in terms of the flow intensities or the transition intensities, as the case may be, between the states. Specifically, incidence-independence is defined as equality of the intensities $S_0 \to S_4$, $S_2 \to S_6$, $S_2^{(1)} \to S_6^{(1)}$, etc., equality between $S_0 \to S_2$ and $S_4 \to S_6$, equality between $S_2 \to S_2^{(1)}$ and $S_6 \to S_6^{(1)}$, etc. Mortality-independence is defined with the help of (4) or (4′) and similar relations.

4. SOME CONSEQUENCES OF THE MATHEMATICAL MODELS

Of the deterministic model based on figure 1, section 3, we shall seek a steady state solution, *i.e.*, a solution based on the assumption that the x_i are constant in time. This would be a representation of a population in dynamic equilibrium. In order to keep the system in a steady state, the hypothetical substance substituted for the population has to be supplied into state S_0 at a constant rate, say b. In a human population b would be the birth and immigration rate. For convenience of notation, for each S_i we define Q_i by

$$Q_i = \sum_j q_{ij}. \tag{5}$$

In a steady state the flow into any state S_i equals the flow out of that state. This leads to the following system of 4 equations:

$$\begin{aligned} x_0 Q_0 &= b & x_4 Q_4 &= x_0 q_{04} \\ x_2 Q_2 &= x_0 q_{02} & x_6 Q_6 &= x_2 q_{26} + x_4 q_{46}. \end{aligned} \tag{6}$$

These 4 equations determine the "state frequencies" x_i if the transition intensities q_{ij} and the birth and immigration rate b are given. In fact, to each set of positive b and q's there corresponds a unique set of positive x's. However, the q_{ij} are unobservable whereas, in principle, the x_i can be measured. It is therefore more realistic to consider the x_i as known, and (6) as a system of equations in the unknown q_{ij}. Unfortunately, there are fewer equations than quantities q_{ij}, so that some of the latter have to be considered as known in (6). Since there are 4 equations (6), it would seem as if we could arbitrarily select 4 of the q_{ij} to be the unknowns. However, if we select the 4 incidence intensities, then only 3 of the 4 equations (6) turn out to be independent. On the other hand, if we take three incidence intensities and one mortality intensity to be the unknowns, then the 4 equations (6) are independent. For example, with the help of (6) it is possible to com-

pute, say, q_{04}, q_{26}, q_{46} and q_{67} in terms of the remaining q's and the x's, with the result:

$$
\begin{aligned}
q_{04} &= x_0^{-1}[b - x_0(q_{01} + q_{02})] \\
q_{26} &= x_2^{-1}[x_0 q_{02} - x_2 q_{23}] \\
q_{46} &= x_4^{-1}[b - x_0(q_{01} + q_{02}) - x_4 q_{45}] \\
q_{67} &= x_6^{-1}[b - x_0 q_{01} - x_2 q_{23} - x_4 q_{45}].
\end{aligned} \tag{7}
$$

It follows that in order to answer all questions regarding the transition intensities, it is necessary to estimate empirically at least three mortality intensities (*e.g.*, q_{01}, q_{23}, q_{45}) and one incidence intensity (*e.g.*, q_{02}), in addition to the "state frequencies" x_0, x_2, x_4, x_6 and the birth and immigration rate b. The remaining transition intensities can then be computed and questions regarding incidence- and mortality-dependence answered.

It should be remarked that mathematically it is immaterial which incidence intensity and which set of three mortality intensities are chosen to be the known quantities. The choice should therefore depend on practical considerations, and the choice we made above, leading to equations (7), may in a particular situation not be the most practical one. For instance, if q_{67} can be estimated more easily than q_{01}, the latter should appear on the left-hand side of the last equation (7) and the former on the right-hand side of equations (7). Similarly, if, say, q_{46} can be estimated more easily than q_{02}, the third equation (7) should be replaced by a similar equation for q_{02}, whereas q_{46} would appear on the right-hand side of equations (7).

Corresponding to the ratio R_1, given by (1), there are two ratios in our present mathematical model which are of interest:

$$R_2 = \frac{x_0 x_6}{x_2 x_4} \tag{8}$$

and

$$R_3 = \frac{(x_0 q_{01})(x_6 q_{67})}{(x_2 q_{23})(x_4 q_{45})} = \frac{q_{01} q_{67}}{q_{23} q_{45}} R_2. \tag{9}$$

With reference to the discussion in section 2, the ratio R_2 would be taken as a measure of association between the diseases A and B in the FPS composed of all those members of the population that are alive. On the other hand, R_3 represents a similar measure referring to the population of those that died during a specified period of time. With the help of (6), both ratios can be expressed in terms of the transition intensities. For R_2 we get

$$R_2 = \frac{1}{q_{67}} \left(\frac{q_{46}}{q_{02}} Q_2 + \frac{q_{26}}{q_{04}} Q_4 \right) \tag{10}$$

with the Q_i given by (5). R_3 follows after substitution of (10) into (9).

One of the important questions is whether either R_2 or R_3 enables us to decide whether or not the diseases A and B are independent. This question will be taken up more fully in section 5. Here we restrict ourselves to consider what happens if A and B are completely independent (see definition 3). Using (2) and (4) in (10) we obtain

$$R_2 = 1 + Q_0/q_{67} \tag{11}$$

in the case of complete independence. Considering that Q_0 is the relative rate at which healthy persons die or get sick with A or B, whereas q_{67} is the relative death rate of persons sick with A and B, we may expect that in an actual situation Q_0/q_{67} is small compared to unity. If that is the case, then it follows from (11) that R_2 is only slightly greater than unity. That R_2 does not equal unity exactly is a consequence of the fact that in our deterministic treatment we consider in each state a mixture of all age groups. In the probabilistic treatment, which follows next, the fate of a single age group is studied, and it will be seen that the ratio analogous to R_2 has a value exactly equal to unity if A and B are completely independent.

Turning now to the ratio R_3, we see from (9) that the factor by which we have to multiply R_2, in order to obtain R_3, equals $q_{01}q_{67}/(q_{23}q_{45})$. Since q_{01} is the relative death rate of healthy persons, whereas the remaining q's are very nearly the relative death rates of sick persons, we may expect the above ratio to be small compared to unity. As a result, we may expect R_3 to be much less than unity, even in the case of complete independence.

Next we shall treat the stochastic model, based on figure 1 or on figure 2. Let an individual start in state S_0 at time $t = 0$, and let $P_i(t)$ denote the probability of being in state S_i at time t $(i = 0, \cdots, 7)$. In the model of figure 2 we also have the probabilities of being in the states $S_2^{(1)}, S_2^{(2)}, \cdots$, and $S_6^{(1)}, S_6^{(2)}, \cdots$, at time t. Let these probabilities be denoted by $P_2^{(1)}(t), P_2^{(2)}(t), \cdots$, and $P_6^{(1)}(t), P_6^{(2)}(t), \cdots$. In the Appendix a mathematical treatment of the stochastic models will be given, and it will be shown that the following holds if A and B are completely independent:

$$\frac{P_0(t)P_6(t)}{P_2(t)P_4(t)} = 1 \tag{12}$$

The left-hand side of (12) is the probabilistic analogue of the deterministic ratio R_2, defined by (8). We see then that in the stochastic model the ratio of interest is exactly equal to unity in the case of complete independence. In the model based on figure 2 we obtain for any m

$$\frac{P_0(t)P_6^{(m)}(t)}{P_2^{(m)}(t)P_4(t)} = 1. \tag{13}$$

Whereas $P_2(t)$ is the probability of having the disease A at time t for the first time, with B being absent, $P_2^{(2)}(t)$ is the probability of having A at time t for the second time, with B absent, etc. One would probably be most interested in the probability of having A and not B at time t, without qualification on the number of intermediate relapses. Let this probability be denoted by $P'_2(t)$, then

$$P'_2(t) = P_2(t) + P_2^{(2)}(t) + P_2^{(4)}(t) + \cdots.$$

Similarly, let $P'_6(t)$ be the probability of having A and B at time t, without qualification on the number of intermediate relapses. Then from (13) we obtain easily

$$\frac{P_0(t)P'_6(t)}{P'_2(t)P_4(t)} = 1 \tag{14}$$

and again we get the interesting ratio exactly equal to unity.

The probabilistic analogue of the ratio R_3, defined by (9), has the same relation to the ratio on the left-hand side of (12) (or of (14) as the case may be) as R_3 has to R_2, so that the same conclusions hold for this ratio as for R_3.

5. DISCUSSION AND CONCLUSIONS

We return to the question whether the presence or absence of dependence between the diseases A and B can be decided by the value of a ratio like R_2 or R_3, given by (8) and (9), or their probabilistic analogues. First of all it is clear that R_3 is useless, since even in the case of complete independence it is not even close to unity. The same remark applies, of course, to the probabilistic analogue of R_3. Remembering that R_3 is the ratio R_1 given by (1), based on an FPS composed of individuals who have died during a certain time interval, it is possible then to observe a value for this ratio which is much less than unity. One is tempted then to conclude negative association between A and B, (Pearl, '29), whereas in reality A and B may be completely independent.

The following numerical example will illustrate this. It should be understood that the numbers chosen are purely fictitious. Let in a particular year in a certain country (say the United States) the number of individuals of age 30 years (reported age) in the states S_0, S_2, S_4 and S_6 be 1,000,000; 10,000; 10,000 and 100 respectively. The ratio $1{,}000{,}000 \times 100/(10{,}000 \times 10{,}000) = 1$ is in accordance with (12) and is therefore fully compatible with complete independence of A and B. Suppose that indeed A and B are completely independent, and that $q_{01} = .0001$, $q'_{23} = .02$, $q'_{45} = .03$, so that, by (3) and (4), $q_{23} = .0201$, $q_{45} = .0301$ and $q_{67} = .0501$. The expected number of individuals of age 30 years dying during the year of observation in each of the 4 categories is $1{,}000{,}000 \times .0001 = 100$; $10{,}000 \times .0201 = 201$; $10{,}000 \times .0301 = 301$ and $100 \times .0501 = 5$. The cross ratio of these numbers is

$$100 \times 5/(201 \times 301) = .00826$$

which is much less than unity. If we would have based the definition of association on this ratio, we would have concluded strong negative association in flagrant disagreement with our assumption of complete independence in terms of the mathematical model.

Next, let us see how useful the ratio R_2 is, or its probabilistic analogues given by the left-hand sides of (12) and (14). For simplicity of discussion we shall in the following denote by R_2 either of the expressions given by (8) and the left-hand sides of (12) and (14), and we shall pretend that the right-hand side of (11) equals unity exactly. We have shown then in section 4 that complete independence implies $R_2 = 1$, so that at first glance it seems as if this ratio is a meaningful measure of independence. At closer inspection, though, it becomes clear that as a measure of independence R_2 cannot be used. The reason for this is that although complete independence implies $R_2 = 1$, the converse is by no means true. For instance, if we take in (10): $q_{02} = q_{04} = .0001$, $q_{26} = q_{46} = .0002$, $q_{23} = q_{45} = .02$, $q_{67} = .08$ (arbitrary units), then we compute $R_2 = 1.01$, whereas neither (2) nor (4) are fulfilled. As a matter of fact, the particular choice of q's implies that the incidence intensity of, and mortality intensity from disease A, is twice as high in the presence of B as it is in its absence and similarly with A and B interchanged. Thus, there is strong incidence dependence as well as mortality dependence, both in the same direction, but yet the ratio R_2 is very close to unity. Incidentally, in the above example we chose $q_{46}/q_{02} = q_{26}/q_{04}$, which means in words that the presence of B increases the incidence rate of A by the same factor as the presence of A increases

the incidence rate of B. There is little justification for this choice, though, and we may even conceive of the possibility that $q_{46} > q_{02}$ and at the same time $q_{26} < q_{04}$, which would mean that the incidence rate of A is increased by the presence of B (over what it is in the absence of B), whereas the incidence rate of B is decreased by the presence of A. In that case the incidence-dependence of A and B could not any longer be described as either positive or negative.

From the preceding paragraph it would seem that the ratio R_2 is as useless as the ratio R_3 for the problem of investigating possible dependence between the diseases A and B. For, if R_2 is determined empirically, and found to be close to unity, then no conclusion can be drawn at all. However, if R_2 is found to be very different from unity,, then we are able to draw a definite conclusion, namely that the diseases A and B are not independent. The situation is the same here as in many testing problems in statistics, where the power of the test is either unknown, or known to be small for certain classes of alternatives. If the observations lead to acceptance of the hypothesis, we will tend to consider this inconclusive rather than believe that the hypothesis is true. On the other hand, if the observations lead to rejection of the hypothesis, then we do conclude that the hypothesis is false, our confidence in the correctness of this conclusion being inversely proportional to the error probability associated with the hypothesis. In our case, the hypothesis would be that A and B are completely independent, and if the test would be based on R_2 alone, the acceptance region would presumably be an interval about unity. For certain alternatives, such as the one given in the numerical example, the probability of accepting a false hypothesis would be very high.

From the foregoing discussion it follows that it is not completely meaningless to look at the ratio R_2, for if it turns out to be very different from unity we can make a definite decision. However, even if this happens, we can only infer that A and B are not completely independent, but we cannot tell in which way they are dependent. It follows then that in order to answer all questions concerning dependence, it is not sufficient to observe only R_2. With reference to section 4, specifically equations (7), it is necessary not only to estimate empirically x_0, x_2, x_4 and x_6, but also three mortality intensities and one incidence intensity, *e.g.*, q_{01}, q_{23}, q_{45} and q_{02}. Then and only then can all questions regarding dependence be settled. It should be remarked that this situation is bad, because it requires data of a kind not usually available.

The conclusions of the preceding paragraph were drawn under the

presumption that the observations are made either on a population of mixed ages, or on one narrow age group. In either case one obtains fewer equations than unknown transition intensities q_{ij}. The situation may possibly improve considerably if observations are made on several age groups. With reference to the stochastic model based on figure 1, section 3, suppose that the assumptions concerning the dependence of the q_{ij} on t, u and v are reasonably simple, *i. e.*, involving some, but not too many parameters, and suppose that the $P_i(t)$ $(i = 0, 2, 4, 6)$ are computed in terms of the unknown parameters and t. Keeping in mind that mortality data are more easily available than morbidity data, we can equate the theoretical expressions for the expectations of the various death rates, such as $P_0(t)q_{01}(t)$, $P_2(t)q_{23}(t)$, etc., to the observed death rates for age t. If death rate data are available for enough age groups, then possibly enough equations are obtained to make possible the estimation of the unknown parameters in the functions q_{ij}. This needs further investigation.

APPENDIX

Mathematical treatment of the stochastic models

First, it will be indicated how an explicit solution can be obtained to a Markov process represented by a diagram which has no closed paths. The diagrams in figures 1 and 2 satisfy this requirement. The solution may be obtained at once in the form of certain integrals, without the necessity of writing down and solving differential equations. For simplicity the method will be illustrated for the process represented by the diagram in figure 1 and only in the case of complete independence. The treatment of the more general situations wil lthen be obvious.

The method starts by introducing certain conditional densities and certain functions which may be called "survival functions." Remembering that, in section 3, u was defined as the time at which the transition $S_0 \rightarrow S_2$ is made, if it does in fact occur, we introduce the conditional density $p_2(u \mid t)$ of u, given that at t the individual is in state S_2 (obviously $p_2 = 0$ unless $u \leqq t$). The densities $p_4(v \mid t)$ and $p_6(u, v \mid t)$ are defined in a similar way. The notation of section 3 will be changed slightly: q_{01}, q'_{23} and q'_{45} will be replaced by q_1, q_3 and q_5 respectively, $q_{02} = q_{46}$ by q_2 and $q_{04} = q_{26}$ by q_4. It should be remembered that all q_i depend on t: q_3 depends also on u and q_5 depends also on v. In order to simplify the writing we shall suppress in the notation the dependence of q_3 on u and of q_5 on v. The following functions are introduced:

$$L_i(t_1, t_2) = \exp[-\int_{t_2}^{t_2} q_i(x)\,dx] \qquad i = 1, \cdots, 5. \tag{15}$$

Obviously the functions L_i satsfy the following property:

$$L_i(t_1, t_2)L_i(t_2, t_3) = L_i(t_1, t_3) \quad \text{if} \quad t_1 \leqq t_2 \leqq t_3. \tag{16}$$

Finally we introduce the following functions:

$$M_0 = L_1L_2L_4, \quad M_2 = L_1L_3L_4, \quad M_4 = L_1L_5L_2, \quad M_6 = L_1L_3L_5. \tag{17}$$

Analogous to (16) we have

$$M_i(t_1, t_2)M_i(t_2, t_3) = M_i(t_1, t_3) \text{ if } t_1 \leqq t_2 \leqq t_3 \quad (i = 0, 2, 4, 6). \tag{18}$$

$M_i(t_1, t_2)$ is the probability that an individual who is in the state S_i at t_1, is still in S_i at t_2 $(t_1 \leqq t_2,\ i = 0, 2, 4, 6)$. The functions M can therefore be called "survival functions." With the help of these functions, solutions to the Markov process are readily obtained. Obviously we have

$$P_0(t) = M_0(0, t). \tag{19}$$

The probability that the individual is in S_2 at t and made the transition $S_0 \to S_2$ in the time interval $(u, u + du)$ is $P_2(t)p_2(u \mid t)\,du + o(du)$. On the other hand, for this to happen the individual has to stay in S_0 until u, which happens with probability $M_0(0, u)$; then he has to make the transition, which happens with probability $q_2(u)\,du + o(du)$; and then he has to stay in S_2, which happens with probability $M_2(u, t) + o(1)$. This leads to the equation

$$P_2(t)p_2(u \mid t) = M_0(0, u)q_2(u)M_2(u, t). \tag{20}$$

Similarly we obtain

$$P_4(t)p_4(v \mid t) = M_0(0, v)q_4(v)M_4(v, t). \tag{21}$$

$$\begin{aligned} P_6(t)p_6(u, v \mid t) &= M_0(0, u)q_2(u)M_2(u, v)q_4(v)M_6(v, t) \text{ if } u < v \\ &= M_0(0, v)q_4(v)M_4(v, u)q_2(u)M_6(u, t) \text{ if } u > v. \end{aligned} \tag{22}$$

$P_2(t)$ is obtained by integrating the right-hand side of (20) with respect to u. Similarly, $P_4(t)$ results from integrating the right-hand side of (21) with respect to v and $P_6(t)$ from integrating the right-hand side of (22) over both u and v, using the first equation in the region $u < v$, the second in the region $u > v$. By using (17) and (18), equation (12) can now easily be established.

The treatment of more general situations, for example, the case when A and B are not completely independent, follows the same lines as illustrated in the example just given.

If one would only be interested in deriving equations (12), (13) and (14) in the case of complete independence, then it is possible to do this by an elegant method, suggested by Mr. J. Karush (private communication), which obviates the necessity of deriving first explicit expression for the $P_i(t)$. For simplicity we shall give the derivation for the process represented in figure 1, but the type of proof can equally well be used for more complicated processes, such as the one represented by figure 2. If A and B are completely independent, then the resulting Markov process is the superposition of three completely independent processes, which we shall denote by I, II and III: I is a Markov process with two states: a live and a dead state, and a transition intensity $q_1(t)$ from one to the other. II is a Markov process with three states: alive without disease A, alive with A, and dead from A; with transition intensities $q_2(t)$ and $q_3(t,u)$ respectively. III is a Markov process with three states: alive without B, alive with B, and dead from B; with transition intensities $q_4(t)$ and $q_5(t,v)$. Let the random variable T_1 be the transition time in process I. Similarly, let U and T_2 be the two transition times in II, V and T_3 in III. We have then that T_1, (U,T_2) and (V,T_3) are completely independent. Let S_a denote the state of being alive, S_A the state of being alive with A (B may or may not be present), S_B the state of being alive with B (with or without A), and S_{AB} the state of being alive with both A and B, all at time t. Thus, S_{AB} coincides with S_a. We have

$$P\{S_A \mid S_a\} = P\{U < t \mid T_1 > t, T_2 > t, T_3 > t\} = P\{U < t \mid T_2 > t\}$$

by independence. Similarly, $P\{S_B \mid S_a\} = P\{V < t \mid T_3 > t\}$. Finally,

$$\begin{aligned} P\{S_{AB} \mid S_a\} &= P\{U < t, V < t \mid T_1 > t, T_2 > t, T_3 > t\} \\ &= P\{U < t \mid T_2 > t\} P\{V < t \mid T_3 > t\} = P\{S_A \mid S_a\} P\{S_B \mid S_a\}. \end{aligned}$$

In words: given that an individual is alive at t, the property of having A is independent of the property of having B. From this, (12) follows easily. It is also possible to write down expressions for the $P_i(t)$ in terms of the random variables introduced above. For example: $P_2(t) = P\{T_1 > t\} \cdot P\{U < t, T_2 > t\} P\{V > t\}$. This also leads immediately to (12).

SUMMARY

The paper is concerned with a description and analysis of two different methods of defining the concept of association between two diseases A and B. The first method (section 2) is based on the classification of a well-defined group of individuals into four categories, according to their A-B disease pattern, *i. e*, those who have neither A nor B, those who have A only, those who have B only, and those who have both A and B. Different choices for this group of individuals may lead to contradictory conclusions as regards to association. The second method of definition of association (section 3) is based on a mathematical model of the phenomenon of acquiring diseases A and B and succumbing to them. The second method seems to be more meaningful than the first. A few simple mathematical models—both deterministic and stochastic—are presented, and some consequences drawn. The mathematical treatment of the stochastic models is included in the Appendix.

Two concepts have to be distinguished: incidence-independence and mortality-independence. It is shown in sections 4 and 5 that in order to assess completely the types and amount of dependence between A and B, it is not sufficient to compute a simple cross ratio from the classification of individuals into 4 categories according to their A-B sickness pattern. Some suggestions are made regarding the types of observations which would have to be made in order to answer all questions pertinent to the association between A and B.

ACKNOWLEDGMENTS

The author is highly indebted to all those participants in the Research Seminar on Statistical Problems in Health whose thoughts and suggestions have been incorporated in this paper, especially Drs. J. Neyman, D. R. Cox, J. Karush, Agnes Berger, Elizabeth L. Scott and W. Smith.

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BOOK REVIEWS

Anthropology and Human Nature. By M. F. Ashley Montagu. 390pp. Porter Sargent, Boston, 1957. $6.00.

I have a friend who runs a restaurant, quite successfully so. The secret of his success, he says, is a wise use of left-overs. In an analogous sense Prof. Montagu is also successful as a purveyor of literary comestibles. This volume is another of the very palatable and digestible *ragout à la Montagu,* a specialty of the author. To those of us who keep pace with his considerable output there is a lot of rehashing in the concoction. Don't get me wrong! I'm all for this sort of thing. However, the element of surprise is not in content, per se, but in the way the volume is put together.

No far-seeing social scientist will disagree with the main theme of the book: to put into operation within the cultural framework the findings of social science, so that the social scientist is in effect a "social engineer." To close the gap between theory and practice is a defensible aim. The real issue is the definition and elucidation of a "finding" as fact rather than as opinion. Montagu, to judge by his very extensive bibliographies, reads widely. He has a flair for synthesis and restatement that cannot be denied. Personally, I learn a lot from what he brings together. But I'm not always sure, or clear, if the statements made are evidence or support; evidence in the sense of objective data, support in the sense of subjective (re)-interpretation. I have the feeling—as I have had in his earlier works—that he tries too hard to do away with "race" and substitute "ethnic group." The problem is not simply a pre- or post- genetic viewpoint. It is, I think, a confusion between human groups as biologic units and human groups as socially interacting units—not what Man is, but what men do about it! Montagu's logic seems to be that to do away with "race" is to do away with a major cause of human group tension and competition; this, in turn, bolsters his idea that Man is innately an organism that seeks species survival and, hence, is instinctively against intra-*sapiens* conflict.

In 1946 the late Raymond Pearl (*Man the Animal*) neatly analyzed the relative variability of normal adult human beings. If size and shape dimensions be rated as 1.0, then physiological dimensions = 1.8, weights (alimentation factor) = 3.4, motor and sensory performance = 9.3, judgment = 47.4, and behavior = 135.5. To put it succintly, human

behavior is over 100 times more variable than human biology. I see no way in which a substitution of terms will militate against this sort of picture. Competition (or war, if you will) between groups is not a matter of biology. It is one of mental outlook, habits, ways of doing, and so on—the warp and woof of human behavior as packaged into culture. And no fooling around with words will alter this!

The Chapter on "Sexual Development and Sex Beliefs" leans heavily upon his 1946 "Adolescent Sterility" which in 1957 was greatly expanded into "The Reproductive Development of the Female"—another excellent job of restatement plus up-dating and evaluation.

The Chapter on "Crime" finally beats to death the tired old horse of Hooton's *Crime and the Man.*

The book ends with two bibliographies, one of 17 pages pertinent to the data in the book (by other authors), one of 12 pages (equally pertinent) of writings by Montagu.

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Effect of Radiation on Human Heredity. 168 pp. WORLD HEALTH ORGANIZATION. Geneva, Switzerland, 1957. $4.00.

Some ionizing radiation exists, varying in amount in different geographical areas, as a part of man's natural environment. Recent technological developments opened up new, potent, man-made sources of ionizing radiations. The biologists are aware of the potential dangers to the health of the present, and, perhaps even more so, of the future generations. They are engaged in intensive search regarding the probable effects of ionizing radiations on the descendants of individuals and of groups of individuals exposed to increased amounts of such radiations. This scrutiny has been carried on for some time by scientists of different nations.* In view of the community of interest and the fact that some

* Cf. 1) BONE AND RADIOSTRONTIUM. By Arne Engström, Rolf Björnerstedt, Carl-Johan Clemedson and Arne Nelson. 139 pp. John Wiley, New York, 1957. No price indicated. 2) BIOLOGICAL EFFECTS OF WHOLE-BODY GAMMA RADIATION ON HUMAN BEINGS. By Harold O. Davidson. 101 pp. Johns Hopkins Press, Baltimore, 1957. $4.50. 3) THE ATOMIC AGE AND OUR BIOLOGICAL FUTURE. By H. V. Brøndsted. Translated by E. M. Huggard. xiv + 80 pp. Philosophical Library, New York, 1957. $2.75. 4) OUR NUCLEAR ADVENTURE. By D. G. Arnott. xi + 170 pp. Philosophical Library, New York, 1958. $6.00.

radiations can not be limited to the territory of any one nation, it was proper that the subject was taken up by the WHO. An international study group convened in August 1956 at the University of Copenhagen. Its deliberations comprise the present report. Some of the twelve papers deal with various sources of radiation and their possible contribution to genetic damage. Other papers discuss such topics in genetics as effects of inbreeding, estimation of spontaneous mutation rates, and genetic trends in public health.

There is general agreement among the writers that a threshold dose does not exist for genetic damage. In contrast, the organism has the capacity to repair, within limits, the damage resulting from exposure to parts of the body other than the gonads. The ability of the body to recuperate from radiation damage may be illustrated by the following example. Seven hundred *r* (roentgens) of a given quality of x-rays administered in one hour will produce a skin erythema. If the same degree of erythema were to be produced by two doses administered at intervals of 24 hours, each dose would need to be about 535 *r*. Thus a total of 1070 *r* would be necessary to produce the same effect.

The International Commission on Radiological Protection (ICRP), the Medical Research Council of Great Britain (MRC), and the U. S. National Academy of Sciences (NAS) are essentially in agreement on maximum permissible levels of ionizing radiation. They agree that it would be desirable to limit the dose to the gonads of individuals to 5 *r* per year, and to a dose not exceeding 50 *r* from conception to thirty years of age. ICRP recommends that the gonadal dose for the general population should be of the order of background radiation and NAS sets as a maximum permissible gonadal dose 10 *r* to age 30.

It was felt that some radiation sources—such as radioactive waste—will be technologically controlled and that effective measures will be designed to protect those exposed to certain other radiation sources. It was pointed out, however, that accidents and unforseen events may spread materials with a long half-life throughout the general population which would be harmful in hitherto unknown ways.

One author observed that there is no evidence of an increase in the undesirable traits which might be expected should there be an increase in the mutation rate resulting from the expanding use of medical radiology. He emphasized, however, that there may be an increased incidence of leukemia among certain x-ray treated individuals and that this radiation leukemogenesis may be a non-threshold effect analogous to the induction of mutations. It was observed that deaths from leukemia in the general

population are on the increase and may be associated with the increased exposure to ionizing radiation.

Lejeune described three criteria of the genetic influence of radiation: (a) frequency of abnormalities; (b) frequency of still births and miscarriages; (c) variation in the sex ratio. Specifically among children of fathers who were radiologists, as compared with the children of fathers in other medical specialities, the increase of congenital heart disease was found to be significantly higher.

One cannot overemphasize the importance of studying the effects of radiation background on man rather than using only data extrapolated from animal studies. Gapal-Ayengar suggested that studies be carried out in such places as Travancore-Cochin-State in India where the background radiation is considerably higher than in other parts of the world. The nearby areas, with normal background radiation, could provide the comparative data for controlled studies of radiation-induced mutations in man.

To study on a large scale the effects of a rising background radiation, a "Family Register Index," with punch cards containing essentially a family tree, was suggested. Births, deaths, marriage data and offspring would be included. If such data were collected over a ten year period, there would be a million infants born to the marriages under study. Approximately half of these would have at least one brother or sister for comparison. Such a study would also provide valuable experience in handling masses of information which would be needed to evaluate genetic trends in the health of the nation.

Permissible levels of exposure to ionizing radiation are too often thought of as levels which are wholly acceptable and may be taken without undue concern. The authors warned of not gearing a radiological health program to currently accepted levels. We must rather continue to evaluate all areas of possible radiation exposure and genetic damage. It must be kept in mind that the future health significance, just as the national debt, must be considered seriously by this generation for the well being of the coming generations.

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Geography in the 20th Century. Edited by GRIFFITH TAYLOR. xi + 674 pp. Philosophical Library, New York. $10.00.

"When this book was reprinted in 1953 various small revisions and additions were made to the text and two new chapters, XXVI ('Cartography') and XXVII ('The Geographical Interpretation of Air Photography') were added. For the 1957 edition, one new chapter, XXVIII ('The Relations of Geography and History'), has been added and Chapter XIII ('Exploration of Antarctica') brought up to date." So reads the Note to 1957 Edition. For a book with such a time-spanning title, it is difficult to see why the present re-publication merits consideration as an edition, for it is as markedly early twentieth century in its outlook as the original volume.

Chapters by such forward-looking authors as Bowman ("Settlement by the Modern Pioneer"), Peltzer ("Geography and the Tropics") do something to give the work a more constructive outlook, but description, argument as to the nature of geography and its subdivisions, and a deterministic acceptance of environmental dominance still crowd the pages and overshadow the search for basic principles, the scientific sifting of evidence, and the pursuit of order which so increasingly characterize the twentieth century.

To be sure, the chapter on "Environmentalism and Possibilism" strikes out for the liberal attitude in championing those who "without denying the limits every environment sets to man's ambition . . . emphasize the scope of man's action rather than these limits." But even this liberalism apparently sits heavily on the editor's spirit, to judge by the rather cutting interjections he makes as footnotes, notwithstanding that it has almost become conservatism in an age where man confidently expects to break the last remaining tie with his terrestrial environment.

It has been said that no one should become a geographer until he has first excelled in some other branch of science. If geography is to include man in its comparisons of situations at different points on the earth's surface, then a sprinkling of geographers should be drawn from competent human biologists. Until that happens, there seems little chance that geographic texts will sufficiently recognize the limitations of the survey method, the non sequiturs of correlation, and the inconsequence of speculation in the absence of evidence; or that the salutary effects of controlled experiment will be brought to bear upon the biological issues.

Biology was lifted out of the descriptive phase by the genius of

Darwin and Wallace, who saw underlying principles where others saw only cases. Geography badly needs a Darwin!

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The Pharmacology of Psychotomimetic and Psychotherapeutic Drugs. Ed. by S. S. KETY. Annals of the New York Academy of Sciences, *66*, 417-840, 1957.

Techniques for the Study of Behavioral Effects of Drugs. Ed. by P. B. DEWS. Annals of the New York Academy of Sciences, *65*, 247-356, 1956.

The Neurohypophysis. Ed. by H. HELLER. xv + 275 pp. Butterworth Scientific Publications, London, 1957. $7.00.

In fairness to authors and publishers a statement concerning the specific merits of the three books must be made before I attempt to consider in a more general manner the problem raised by these and closely related works.*

The volume *The Pharmacology of Psychomimetic and Phychotherapeutic Drugs* brilliantly organized by S. S. Kety deals with the action of drugs which, like lysergic acid, mimic symptoms occurring in mental disease and those which, like the tranquillizers, are used for therapeutic purposes. The clinical experiences are described briefly whereas the experimental work is reviewed in considerable detail from the point of view of the neurophysiologist, biochemist and psychologist. The section on serotonin and its relation to mental diseases makes fascinating read-

* Cf. 1) PSYCHOTROPIC DRUGS (Proceedings of the International Symposium on Psychotropic Drugs, Milan, May 9-11, 1957). Ed. by S. Garattini and V. Ghetti. xiv + 606 pp. Elsevier Publ. Co., Amsterdam, 1957. $19.50. Distributed by D. Van Nostrand Co., Princeton, N. J. One section is devoted to behavioral effects. 2) NEUROPHARMACOLOGY. Edited by Harold A. Abramson. 381 pp. Josiah Macy, Jr. Foundation, New York, 1957. $4.50. 3) PSYCHOPHARMACOLOGY. Edited by Harry H. Pennes. xiii + 362 pp. Hoeber-Harper, New York, 1958. $8.00. 4) THE RELATION OF PSYCHIATRY TO PHARMACOLOGY. By Abraham Wikler. viii + 322 pp. Williams & Wilkins, Baltimore, 1957. $4.00. 5) PHARMACOLOGY IN MEDICINE. Edited by Victor A. Drill. xi + 1273 pp. McGraw-Hill, New York, 1958. $19.50. Part seven (pp. 309-334) on "Drugs Affecting Behavior" was contributed by Peter B. Dews.

ing. Among the neurophysiological papers the essay of H. Grundfest on bioelectrical phenomena is of considerable value beyond the specific purposes of this monograph.

The *Techniques for the Study of Behavioral Effects of Drugs* is a misnomer insofar as the book covers not only techniques but also, in some detail, the action of these drugs. It supplements (and overlaps in part with) the previous volume which in one section is concerned with the behavioral effects of drugs. In the "schedule-oriented operant technique" developed by Skinner and his school the rat is trained to press a bar to obtain food. The performance (rate of pressing) depends on the schedule of reinforcement which is varied widely. The ingenious recording technique permits the accumulation of enormous quantities of data and the demonstration of the effects of various drugs on this performance. This technique has been combined with sensory discrimination in the pigeon in which the pecking response is utilized (Blough). N. E. Miller advocates and practises the application of several behavioral measures in order to avoid the pitfalls due to the exclusive usage of a single response. The development of this branch of research and its application to the problem of behavior and mental disease has been so rapid that some caution seems advised as expressed by M. Sidman in this symposium, who believes that "the discovery of relations between behavior and other biological phenomena will lead inevitably to the elimination of a great deal of psychopharmacologic investigation that now seems exciting but is actually little more than aimless wandering when compared to future potentialities in this field."

The third volume *The Neurohypophysis* edited by H. Heller is likewise a symposium. Its scientific level is very high, and the point of view brought to bear on the neurohypophysis is very broad. Anatomical (including comparative anatomy), physiological, pharmacological and biochemical investigations are reported. This work is highly recommended to those interested in neuro-endocrine relations.

The rapid pace of recent scientific advancements accounted for, in part, by large scale government support has led to a considerable increase in the number of published symposia. Their value for the scientific worker is obvious, but Bertrand Russell's remark: "If a book is to have value except for a work of reference it must be the work of one mind" should not be forgotten. Only then synthesis can be achieved in problems which like those dealt with in these three symposia are obviously concerned with organismic functions of highest complexity.

The great appeal which psychopharmacology exerts on investigators

lies not only in its new approach to the problem of mental illness but also in the fact that these drugs permit the normal individual to observe in himself alterations in "psychic" functions leading to experiences which Osmond describes as "most strange, most awesome, and among the most beautiful things in a varied and fortunate life. These are not escapes from but enlargements, burgeonings of reality."

The question arises now whether the alterations of psychic functions by psychomimetic and psychotherapeutic drugs are understandable within the framework of neurophysiological concepts which seem to account, to some degree, for such fundamental psychic processes as emotion and perception. The previous work of the writer (*Physiological Foundations of Neurology and Psychiatry*, 1953, and *Autonomic Imbalance and the Hypothalamus: Implications for Physiology, Medicine, Psychology, and Neuropsychiatry*, 1957, both published by the University of Minnesato Press) suggests that:

1. Emotional excitement is associated with an excitation of the hypothalamus. Its posterior division discharges "downward" and activates the somatic and particularly the sympathetic division of the autonomic nervous system.

2. An "upward" discharge from the hypothalamus influences the cerebral cortex as a whole. This discharge interacts in the specific sensory projection areas with sensory impulses from eye, ear, etc. This interaction is essential for perception.

3. Changes in cortical functions alter in turn the degree of excitability of the hypothalamus and thereby the intensity (and also the quality †) of the hypothalamic-cortical discharge.

4. Changes in the excitability of the posterior hypothalamus are associated with corresponding changes in the intensity of the upward- and downward discharges.

Applied to the problem of psychopharmacological action one would expect that drugs acting on the hypothalamus directly or indirectly (via the cortex) would produce parallel changes in psychic and autonomic processes (i. e., in up-and downward discharges). It is interesting to note that several drugs alter autonomic and psychic events in the expected manner. Thus lysergic acid (LSD) causes pronounced excitatory psychic effects and sympathetic discharges, whereas 2-brom LSD is without effect

† Concerning the qualitative changes see the above cited monograph (1957) and my paper Acta Physiol. Pharmacol. Neerland. *6*: 111, 1957.

on the sympathetic system and the psyche (Rothlin). Another psychomimetic drug (mescaline) is likewise activating the sympathetic system, whereas reserpine depresses psychic functions and diminishes sympathetic discharges.

Thus a relatively simple scheme brings some coherence into the mass of data obtained in different species while normal and abnormal "psychic" processes occurred. It remains to be seen whether this scheme will be confirmed by, and helpful in, future investigations.

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An Appraisal of the Longitudinal Approach to Studies of Growth and Development. By DANKWARD KODLIN and DONOVAN J. THOMPSON. 47 pp. Purdue University, Lafayette, Indiana. Monographs of the Society for Child Development, Serial No. 67, 1958. No price indicated.

In the early years of the present century, students of growth repeatedly emphasized the importance of longitudinal studies in which each subject is measured repeatedly over a period of time. As a result, several such studies were set up, first in the United States and later elsewhere. Some of these studies have now accumulated information on many individuals over a period extending from early childhood to adulthood. The problems, both practical and statistical, of reducing this mass of information into a coherent story are acute and progress in solving them has sometimes seemed disappointing. It is not surprising therefore that a certain reaction against an uncritical dependence on longitudinal data should have set in, and the Apprasial seems to have originated in this way. It claims to answer the tough question "When are the longitudinal and the cross-sectional approaches interchangeable, if at all?"

The first half of the pamphlet presents a list of criteria—all fairly obvious—by which an investigator can decide whether his problem necessitates a longitudinal study, followed by a very brief historical review and a description of the programs in operation at the Harvard University School of Public Health, the Fels Research Institute and the Child Research Council, Denver. The comments on these studies em-

phasize the "pernicious results of long-term accumulation of data"—collector's instinct has too often led to the collection of figures whose ultimate purpose is never adequately considered, a criticism which should by no means be confined to longitudinal studies.

The second part of the monograph compares methods of analysis of cross-sectional and longitudinal data and their efficiencies in various respects. A good deal of needlessly elaborate mathematics is used to establish some rather obvious conclusions, which amount in summary to saying that the results of cross-sectional and longitudinal studies in many aspects agree, apart from sampling errors. When sampling considerations are introduced, the authors discuss longitudinal studies in which subjects enter and leave during the course of the program; they reproduce the formulae from Cochran's textbook without considering too closely their appropriateness in the present context. No mention is made of the basic paper on this problem by Patterson (J.Roy.Statist. Soc.B,. *12*, 241, 1950) and only passing reference is made to Tanner's detailed exposition of Patterson's results in anthropometric terms (Hum. Biol., *23*, 93, 1951). An italicized conclusion reads "Completely longitudinal records are of no advantage over cross-sectional ones if they are only used to estimate means at particular occasions, and 'mean growth curves' established in either way are equally informative." The first part of this sentence is indeed unexceptable—nobody supposes that longitudinal studies are needed to establish distance standards—but the second part is wildly misleading; the sentence quoted stands over a table showing that a longitudinal sample will often be 10 to 20 times as efficient as a cross-sectional sample in assessing mean growth over a single interval. Shuttleworth's classic monograph of 1937 in the same series seems to have made no impression on the authors!

The present status of longitudinal studies is far from satisfactory, and the authors have done a service by insisting on the necessity of clear aims, continuous working-up of results and scepticism in relation to non-random samples; but an adequate appraisal of the longitudinal approach, with full consideration of its many problems, remains to be written.

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BOOK NOTICES

PRINCIPLES OF PERFECTION. By S. Howard Bartley. xii + 482 pp. Harper, New York, 1958. $6.50. College textbook by a specialist in the study of vision, presenting psychology as a biological science and "meant to be a decided step in getting away from the common persistent retention of mentalistic concepts and usages, while at the same time attempting to recognize the role of awareness (experience, consciousness, etc.)."

SCIENTIFIC SOCIETIES IN THE UNITED STATES. By Ralph S. Bates. ix + 297 pp. Columbia University Press, New York, 1958. $6.50. The text of the useful first edition (1945), dealing with the history and the influence of the scientific societies in the U. S., was supplemented by a new chapter covering the changes that took place in the intervening years (The Atomic Age, 1945-1955). The bibliography (pp. 225-268) was revised and enlarged. Comprehensive index (pp. 269-297).

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY. By Aleck W. Bourne. vii + 348 pp. Little, Brown & Co., Boston, 1958. $8.00. Among the 13 chapters constituting the 9th edition of the *Advances*, "The Obstetric Pelvis," especially the section on pelvimetry, may be noted.

HIGH-TALENT MANPOWER FOR SCIENCE AND INDUSTRY. By Douglas Brown and Frederick Harbison. 97 pp. Princeton University, Princeton, N. J., 1957. $3.00. "Creative imagination is a gift of but a few in any society. It must be encouraged by understanding support and satisfying use. (It can not be bought at a price but must be developed) through the systematic improvement of a whole complex of cultural, educational, and industrial institutions and processes." The two essays appraise relevant policies at home and abroad.

INTRODUCTION TO THE THEORY OF DETERMINANTS AND MATRICES. By Edward Tankard Browne. xi + 270 pp. University of North Carolina Press, Chapel Hill, 1958. $7.50. Attempting to avoid an excessively abstract approach the author presents the fundamental facts, together with proofs and illustrations, keeping in mind not only students of mathematics but also the students from "foreign fields."

MULTIVARIATE CORRELATIONAL ANALYSIS. By Philip H. DuBois. xv + 202 pp. Harper & Brothers, New York, 1957. $4.50. Though written with special reference to social science research, the presentation will be found useful by workers in human biology who frequently observe and experiment within multivariate contexts. Both multiple correlation and multiple "factor analysis" are considered.

MINNESOTA STUDIES IN THE PHILOSOPHY OF SCIENCE. Vol. II. Edited by Herbert Feigl, Michael Scriven and Grover Maxwell. xv + 553 pp. University of Minnesota Press, Minneapolis, 1958. $7.00. The volume presents further

results of work at the Minnesota Center for the Philosophy of Science on philosophical and methodological problems of science, with special reference to psychology. Feigl's paper on the "mental" and the "physical" stands out on account of its size (pp. 370-497) and thoroughness of analysis.

SCHEDULES OF REINFORCEMENT. By C. B. Ferster and B. F. Skinner. 741 pp. Appleton-Century-Crofts, New York, 1957. $6.50. "When an organism acts upon the environment in which it lives, it changes that environment in ways which often affect the organism itself. Some of these changes are . . . "reinforcers": they increase the likelihood that the organism will behave in the same way again." This is a detailed report on the effect of varying the ways in which the reinforcements are scheduled. Most of the data refer to pigeons' pecking a key on the wall of an experimental chamber but the methodology has important applications for the analysis of the control of human behavior. A glossary is appended.

ANCIENT AND MODERN MAN IN SOUTHWESTERN ASIA. By Henry Field. xiii + 342 pp. University of Miami Press, Coral Gables, Fla., 1956. No price indicated. Based on 3 decades of library research and field work, the volume summarizes present knowledge on 12 areas (Sinai, Israel, Jordan, Lebanon, Syria, Turkey, Caucasus, Iraq, Arabian Penninsula, Iran, Afghanistan, and Baluchistan), considering 1) geography (incl. climate, water supply, vegetation, fauna, natural resources), 2) ancient man, and 3) modern man. Appendixes contain extensive anthropometric data (especially stature and cranial measurements and indices).

BIBLIOGRAPHY ON SOUTHWESTERN ASIA: IV. By Henry Field. xlvi + 464 pp. University of Miami Press, Coral Gables, Fla., 1957. No price indicated. This is the fourth in a series of specialized bibliographies covering the region indicated in the title (from Egypt to Indus Valley in West Pakistan, and from Anatolia and the Caucasus to the Arabian Sea). Emphasis is placed on anthropogeography (over 8,000 titles, listed alphabetically by author). There is an author index but no subject index.

HUMAN TYPES. By Raymond Firth. vi + 224 pp. Barnes & Noble, Inc., New York, 1957. $2.25. Revised edition of an introduction to social anthropology, first published in 1938. The first chapter deals with racial traits and mental differences.

MINERAL NUTRITION AND THE BALANCE OF LIFE. By Frank A. Gilbert. xv + 350 pp. University of Oklahoma Press, Norman, 1957. $5.95. Designed to supplement the author's "Mineral Nutrition of Plants and Animals" (1948). Includes subject matter not originally covered, such as the history and geographical distribution of the deficiencies of individual minerals. In the body of the text, human nutrition is treated only incidentally (especially in connection with iodine). The last chapter (pp. 256-263) considers briefly some of the implications of mineral nutrition for man.

ATOMIC ENERGY IN MEDICINE. By K. E. Halnan. ix + 157 pp. Philosophical Library, New York, 1957. No price indicated. A readable introduction to a rapidly expanding field.

TUBERCULOSIS IN WHITE AND NEGRO CHILDREN. Vol. I. By Janet B. Hardy. vii + 122 pp. Vol. II. By Miriam E. Brailey. 103 pp. Harvard University Press, Cambridge, 1958. $7.50 and $4.50. Volume I presents the roentgenological, Volume II the epidemiological aspects (prognosis of tuberculosis infection, the risk of developing reinfection) of a study originated in Baltimore in a special outpatient clinic in 1928, with follow-ups continued to 1950. The mean annual reinfection rate among Negro children was ten times the rate noted for white children.

CLIMATOLOGY. By W. G. Kendrew. xv + 400 pp. Oxford University Press, New York, 1957. 42 s. Protective devices available to modern civilized man tend to obscure the fact that "climate is the most fundamental and far-reaching of the natural elements which control life." The book, the first edition of which appeared in 1949, deals with temperature, atmospheric pressure and winds, water in the atmosphere and its condensations and climatic types.

INITIATION AUX MÉTHODES STATISTIQUES EN BIOLOGIE. By Maxime Lamotte. 144 pp. Masson & Cie, Paris, 1957. 2,000 fr. An introductory text by a professor of zoology at the Faculty of Sciences (Paris).

OBJECTIVE TESTS AS INSTRUMENTS OF PSYCHOLOGICAL THEORY. By Jane Loevinger. 59 pp. Psychological Reports, Missoula, Mont., 1957. $2.50. A thoughtful monograph centered around the concept of "construct validity" of psychological tests, defined in terms of content, internal structure and relation to outside variables. The author stresses the need for the recognition of psychometrics as the handmaiden of psychology rather than merely of psychotechnology.

SYSTEMATIC SOCIOLOGY. By Karl Mannheim. Edited by J. S. Eros and W. A. C. Stewart. xxx + 169pp. Philosophical Library, New York, 1957. $6.00. The post-humous edition of "An introduction to the study of society" consists of four parts dealing, respectively, with man's psychological equipment (with emphasis on the flexibility of behavior), elementary social processes, social integration, and factors which make for social stability and change.

A HISTORY OF NUTRITION. By Elmer Verner McCollum. x + 451 pp. Houghton Mifflin, Boston, 1957. $6.00. Covers, approximately, the period 1740-1940 and considers "the efforts of the apothecary type of chemists to learn about the constituents of plant materials; of physiologists who made the early digestion studies; of the occasional penetrating studies of chemists which brought order out of chaos in comprehending the chemical phenomena of the organic kingdom of nature; and also of the feeding studies of the animal husbandry type of investigator, and of the progressively well-controlled studies on men and animals, which made the science of nutrition."

BASIC NUTRITION. By E. W. McHenry. xv + 389 pp. J. B. Lippincott, Philadelphia, 1957. $6.00. A college textbook, growing out of 30 years of experience in research and teaching in the field of nutrition. The author is professor of public health nutrition at the University of Toronto.

CHEMOTHERAPY AND THE CENTRAL NERVOUS SYSTEM. By Henry McIlwain. viii + 328 pp. Little, Brown and Company, Boston, 1957. $10.00. In recent years rapid, almost precipitous developments took place in the chemotherapeutic approach to mental disorders. The author attempted to place them in proper historical perspective and portray them in a wider setting. "There is thus recounted a subject to which chemistry, biochemistry, pharmacology, physiology and clinical medicine have contributed, and in its presentation the interests of workers and students in each of these subjects has been borne in mind."

CANCER STATISTICS FOR ENGLAND AND WALES 1901-1955. By Alan McKenzie. iv + 99 pp. British Information Services, New York, 1957. $1.04. The core of the volume is the tabular presentation of data relating to cancer at various sites for the period 1901-1955. Secular changes in mortality, cancer in children, regional differences, and survival rates from cancer are considered.

PSYCHOBIOLOGY. By Adolf Meyer. Compiled and edited by Eunice E. Winters and Anna Mae Bowers. xxiii + 257 pp. Charles C. Thomas, Springfield, Ill., 1957. $6.50. The lectures, by an outstanding psychiatrist and thinker, delivered in 1931, are grouped in three sections labelled "Psychobiology" (pp. 3-110), Pathology, and Therapy. The Appendix (pp. 187-214) contains a welcome dictionary of Meyer's highly original terminology. Psychobiological data are described in terms of "performances," of integrated processes which are at the same time "physical" and "mental." Psychobiology studies organisms behaving with evidences of meaning.

HIGHWAY RESEARCH BOARD BULLETIN 163: NIGHT VISIBILITY. iii + 32 pp. National Academy of Sciences—National Research Council, Washington, D. C. 1957. No price indicated. Four papers, presented at the Board's 36th annual meeting, deal with roadway visibility, highway lighting, safe stopping distance, and visibility of license plates.

BASIC RESEARCH: A NATIONAL RESOURCE. viii + 64 pp. National Science Foundation, Washington, D. C., 1957. $.45. Prepared and transmitted to the President of the United States in the interest of achieving desirable balance between basic research—a continuing search for new knowledge—and the applications of science to defense, health, and the economy. Portrays the use of basic research, its contemporary status in the U. S. A., and the steps to be taken in strengthening the appeal and opportunities for exploring the unknown.

FEDERAL GRANTS AND CONTRACTS FOR UNCLASSIFIED RESEARCH IN THE LIFE SCIENCES. v + 241 pp. National Science Foundation, Washington, D. C., 1957. No price indicated. The fourth annual report covers the fiscal year 1956. The projects are listed under one of the 20 categories (such as "Structural Biology," "Methodology,"" and "Equipment Design"), and subdivided by state and institution. There is no overall subject or name index which would facilitate orientation.

THE ORIGIN OF LIFE ON THE EARTH. By A. I. Oparin. Translated from the Russian by Ann Synge. xviii + 495 pp. Academic Press, New York,

1957. $6.80. The topic has been of active concern to the author for well over three decades, his first book on "Origin of Life" having appeared in 1924. The expanded presentation was translated into English by Professor Sergius Morgulis (Macmillan, 1938; Dover, 1953). Now the third, enlarged edition of this thorough, experimentally oriented treatise is being made available in English.

PROGRESS REPORT IN CHEMICAL LITERATURE RETRIEVAL. Edited by Gilbert L. Peakes, Allen Kent and James W. Perry. xii + 217 pp. Interscience Publishers, Inc., New York, 1957. $4.75. Effective utilization of recorded knowledge is becoming as important and challenging task as adding new knowledge. The first volume in a projected series entitled "Advances in Documentation and Library Science" represents the proceedings of two symposia held under the auspices of the Division of Chemical Literature, American Chemical Society.

THE VERTEBRATE VISUAL SYSTEM. By Stephen Polyak. xviii + 1390 pp. University of Chicago Press, Chicago, 1957. $45.00. This outstanding monograph, a sequel to the author's *The Retina* (1941), begins with a detailed historical review of investigations of the eye and of the visual pathways and centers of the brain (pp. 9-203). It deals with the visual system from the anatomical, pathological and biological point of view, with consideration of its role in the development of man. Numerous illustrations, extensive bibliography (pp. 1059-1358), and detailed index.

PSYCHOLOGICAL DEVELOPMENT THROUGH THE LIFE SPAN. By Sidney L. Pressey and Raymond G. Kuhlen. xxiii + 654 pp. Harper & Brothers, New York, 1957. $6.00. This may be regarded as a second, substantially revised version of an earlier work, entitled *Life: A psychological survey* (1939), presenting developmental psychology in the framework of the total life span, with emphasis on adulthood and old age. The intervening 20 years increased the need for a comprehensive developmental perspective. Growth, change and decline in physique is also considered (pp. 27-69).

ADVENTURES IN MEDICAL EDUCATION. By G. Canby Robinson. xii + 338 pp. Harvard University Press, Cambridge, 1957. $5.00. This is "a personal narrative of the great advance of American medicine" during the last half century by one of its active participants, perhaps best known for his concern with the social aspects of medicine (pp. 253-280).

THE HUMAN SUM. Edited by C. H. Rolph. vi + 232 pp. Macmillan, New York, 1957. $3.75. Eleven essays, gathered at the initiative of the (British) Family Planning Association and directed to two goals: first, improving the health and happiness of British families by ensuring that parents have the children they want and avoid unwanted children; second, educating the British public in their responsibilities in regard to the tremendous problem of world population in relation to world resources.

THE ECOLOGY OF MAN. By Paul B. Sears. 61 pp. University of Oregon Press, Eugene, Ore., 1957. No price indicated. Richly illustrated, the volume "attempts to integrate various points of view by showing that the human ecological process is a resultant of the interactions of cultural patterns with the environmental complex—physical, biological, and social."

CAREER OPPORTUNITIES IN BIOLOGY. By Russell B. Stevens. 63 pp. Publication 552, National Academy of Sciences—National Research Council, Washington, D. C., 1957. $1.00. An effective pamphlet written for young people considering the choice of career.

REASON AND CHANCE IN SCIENTIFIC DISCOVERY. By R. Taton. Translated from French by A. J. Pomerans. 171 pp. Philosophical Library, New York, 1957. $10.00. Using an illustrative rather than excessively systematic approach, the author describes the different realms of scientific discovery (mathematics, theoretical sciences, observational and experimental sciences), the principal factors in the genesis of discovery (systematic analysis, flashes of thought, role of chance and of error) and its various aspects, such as the originality of discoveries.

THE AGING OF POPULATIONS AND ITS ECONOMIC AND SOCIAL IMPLICATIONS. vii + 168 pp. United Nations, Department of Economic and Social Affairs, New York, 1956. $1.75. Considers trends (past, present, and future) in the aging of populations, their causes, and their implications. The Appendix contains tabular information on present age composition of 70 countries and on changes observed over varying lengths of time in 26 countries.

ROOTS OF SCIENTIFIC THOUGHT. Edited by Philip P. Wiener and Aaron Noland. x + 677 pp. Basic Books, New York, 1957. $8.00. "The historian of ideas is interested not only in the logical, cumulative development of scientific thought but also in the extralogical components and affiliations with developments in the history of the arts, of social institution, of religion, and of philosophy. He aims to shed light on the role played by scientific ways of thinking in shaping the course of civilization." The book, prepared by editors of the *Journal of the History of Ideas*, consists of selections from the first 18 volumes of the journal.

THE NEW ERA IN MEDICAL RESEARCH: A SURVEY. Conducted by Douglas Williams Associates. 63 pp. Merck & Co., Inc., Rahway, N. J., 1957. No price indicated. The full subtitle, "A survey of the attitudes [concerning medical research] of some leading people in the field" specifies the nature of the report. The need for research talent, the need for basic research, the lack of effective communication within the field—these are some of the points of agreement in a field characterized otherwise by a high diversity of opinion.

HEREDITY AND YOUR LIFE. By A. M. Winchester. xii + 333 pp. Vantage Press, New York, 1956. $5.00. A popular "account of everyday human inheritance."

THE LIFE OF MAMMALS. By J. Z. Young. xv + 820 pp. Oxford University Press, New York, 1957. $10.00. Presentation of mammalian life, intended for students of biology and medicine. Integrates information provided by anatomy, histology, embryology and physiology. The inital chapter is devoted to "The control of living systems" (pp. 1-30) and is built around the idea of the body as a self-controlling machine, an idea which serves as a unifying theme throughout.